



US009527856B2

(12) **United States Patent**
Braje et al.

(10) **Patent No.:** **US 9,527,856 B2**
(45) **Date of Patent:** **Dec. 27, 2016**

(54) **OXINDOLE COMPOUNDS CARRYING A CO-BOUND SPIRO SUBSTITUENT AND USE THEREOF FOR TREATING VASOPRESSIN-RELATED DISEASES**

(71) Applicant: **AbbVie Deutschland GmbH & Co. KG**, Wiesbaden (DE)

(72) Inventors: **Wilfried Braje**, Ludwigshafen (DE); **Hervé Geneste**, Ludwigshafen (DE); **Wilfried Hornberger**, Ludwigshafen (DE); **Katja Jantos**, Ludwigshafen (DE); **Andreas Kling**, Ludwigshafen (DE); **Claudia Krack**, Ludwigshafen (DE); **Marcel Van Gaalen**, Göttingen (DE)

(73) Assignee: **AbbVie Deutschland GmbH & Co. KG**, Wiesbaden (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/713,824**

(22) Filed: **May 15, 2015**

(65) **Prior Publication Data**

US 2015/0344489 A1 Dec. 3, 2015

Related U.S. Application Data

(60) Provisional application No. 61/993,874, filed on May 15, 2014.

(51) **Int. Cl.**

C07D 471/10 (2006.01)
C07D 295/135 (2006.01)
C07D 305/08 (2006.01)
C07D 401/14 (2006.01)
C07D 487/10 (2006.01)
C07D 209/40 (2006.01)
C07D 213/64 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 487/10** (2013.01); **C07D 209/40** (2013.01); **C07D 213/64** (2013.01); **C07D 295/135** (2013.01); **C07D 305/08** (2013.01); **C07D 401/14** (2013.01); **C07D 471/10** (2013.01)

(58) **Field of Classification Search**

CPC . C07D 471/10; C07D 295/135; C07D 305/08; C07D 401/14; C07D 487/10; C07D 209/40; C07D 213/64

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2014/0194440 A1 7/2014 Braje et al.
2015/0158845 A1 6/2015 Braje et al.

FOREIGN PATENT DOCUMENTS

WO 2009/071689 6/2009
WO 2009/071690 6/2009

OTHER PUBLICATIONS

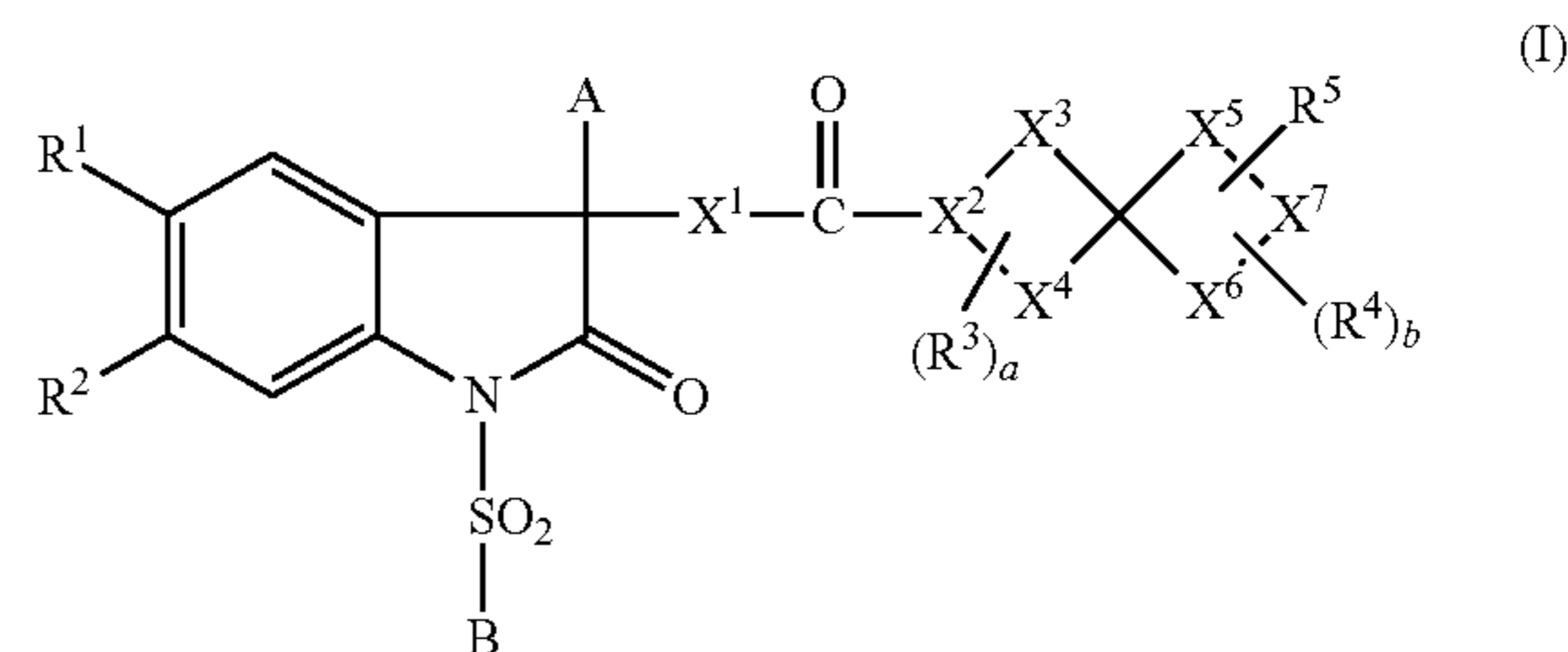
International Search Report for Application No. PCT/EP2015/060761 dated Aug. 3, 2015 (4 pages).

Primary Examiner — Rebecca Anderson

(74) *Attorney, Agent, or Firm* — Neal Gerber & Eisenberg LLP

(57) **ABSTRACT**

The present invention relates to novel substituted oxindole derivatives of formula I



wherein the variables are as defined in the claims and the description. The invention further relates to pharmaceutical compositions comprising compounds I and their use for the treatment of vasopressin-related disorders.

38 Claims, No Drawings

1

**OXINDOLE COMPOUNDS CARRYING A
CO-BOUND SPIRO SUBSTITUENT AND USE
THEREOF FOR TREATING
VASOPRESSIN-RELATED DISEASES**

CROSS-REFERENCE TO RELATED
APPLICATION(S)

This claims priority to U.S. Provisional Patent Application No. 61/993,874, filed on May 15, 2014, the entire contents of which is fully incorporated herein by reference.

The present invention relates to novel substituted oxindole derivatives, pharmaceutical compositions comprising them, and their use for the treatment of vasopressin-related disorders.

Vasopressin is an endogenous hormone which exerts various effects on organs and tissues. It is suspected that the vasopressin system is involved in various pathological states such as, for example, heart failure and high blood pressure. At present, three receptors (V1a, V1b or V3, and V2) via which vasopressin mediates its numerous effects are known. Antagonists of these receptors are therefore being investigated as possible new therapeutic approaches for the treatment of diseases (M. Thibonnier, *Exp. Opin. Invest. Drugs* 1998, 7(5), 729-740; T. Ryckmans, *Current Opinion in Drug Discovery & Development* 13 (2010), 538-547; G. Decaux et al., *Lancet* 371 (2008), 1624-1632; R. Lemmens-Gruber, M. Kamyar, *Cell. Mol. Life Sci.* 63 (2006), 1766-1779).

1-(Het)Arylsulfonyl-1,3-dihydro-2H-indol-2-ones have previously been described as ligands of vasopressin receptors, for example in WO 2005/030755, WO 2006/005609, WO 2006/080574, WO 2008/080970, WO 2008/080971, WO 2008/080972, WO 2008/080973, WO 2009/071687, WO 2009/071689, WO 2009/071690, WO2009/071691, WO 2009/083559, WO 2010/009775 or WO 2010/142739.

Besides the binding affinity for the vasopressin V1b receptor, further properties may be advantageous for the treatment and/or prophylaxis of vasopressin-related disorders, such as, for example:

1.) a selectivity for the vasopressin V1b receptor compared with the vasopressin V1a receptor, i.e. the quotient of the binding affinity for the V1a receptor ($K_i(V1a)$) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor ($K_i(V1b)$) (determined in the unit "nanomolar (nM)"). A larger quotient $K_i(V1a)/K_i(V1b)$ means a greater V1b selectivity;

2.) a selectivity for the vasopressin V1b receptor compared with the vasopressin V2 receptor, i.e. the quotient of the binding affinity for the V2 receptor ($K_i(V2)$) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor ($K_i(V1b)$) (determined in the unit "nanomolar (nM)"). A larger quotient $K_i(V2)/K_i(V1b)$ means a greater V1b selectivity;

3.) a selectivity for the vasopressin V1b receptor compared with the oxytocin OT receptor, i.e. the quotient of the binding affinity for the OT receptor ($K_i(OT)$) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor ($K_i(V1b)$) (determined in the unit "nanomolar (nM)"). A larger quotient $K_i(OT)/K_i(V1b)$ means a greater V1b selectivity;

4.) the metabolic stability, for example determined from the half-lives, measured in vitro, in liver microsomes from various species (e.g. rat or human);

5.) no or only low inhibition of cytochrome P450 (CYP) enzymes: cytochrome P450 (CYP) is the name for a superfamily of heme proteins having enzymatic activity (oxidase). They are also particularly important for the degrada-

2

tion (metabolism) of foreign substances such as drugs or xenobiotics in mammalian organisms. The principal representatives of the types and subtypes of CYP in the human body are: CYP 1A2, CYP 2C9, CYP 2D6 and CYP 3A4. If CYP 3A4 inhibitors (e.g. grapefruit juice, cimetidine, erythromycin) are used at the same time as medicinal substances which are degraded by this enzyme system and thus compete for the same binding site on the enzyme, the degradation thereof may be slowed down and thus effects and side effects of the administered medicinal substance may be undesirably enhanced;

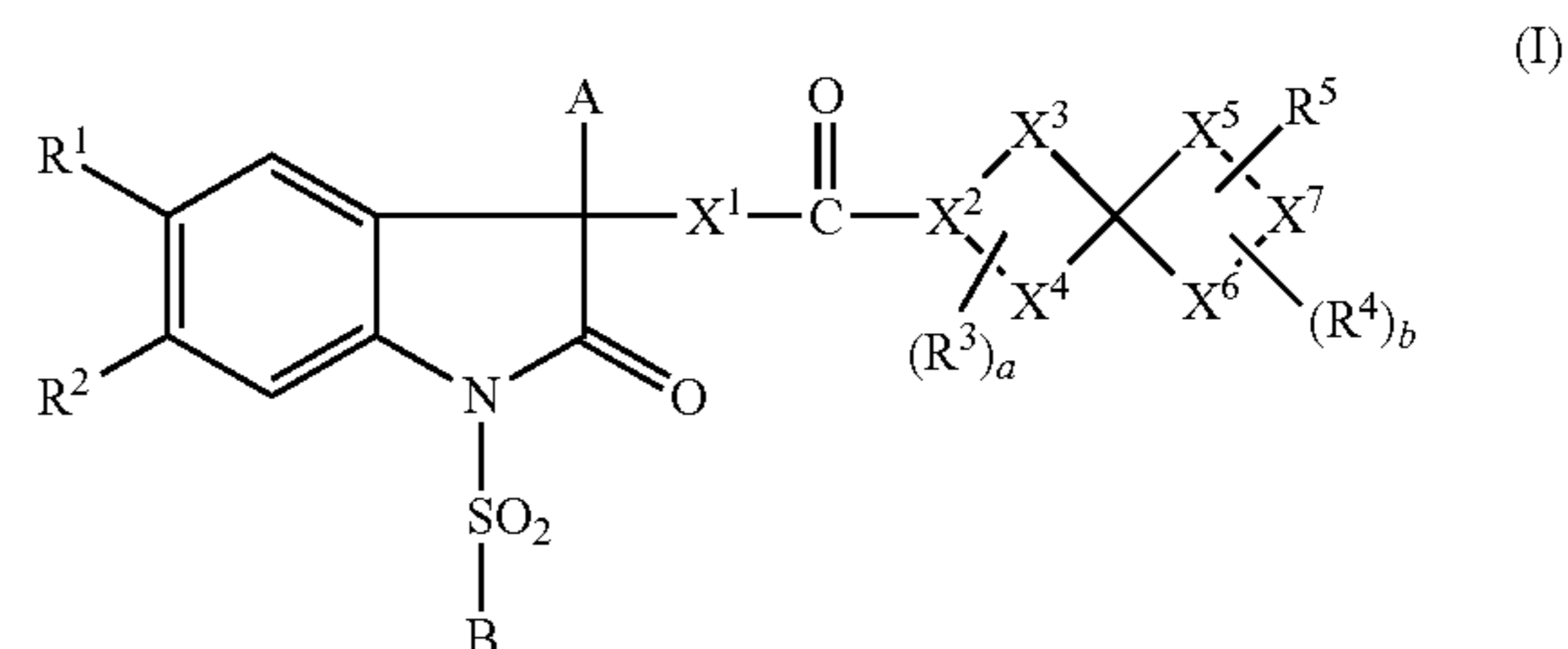
6.) a suitable solubility in water (in mg/ml);

7.) suitable pharmacokinetics (time course of the concentration of the compound of the invention in plasma or in tissue, for example brain). The pharmacokinetics can be described by the following parameters: half-life (in h), volume of distribution (in $l \cdot kg^{-1}$), plasma clearance (in $l \cdot h^{-1} \cdot kg^{-1}$), AUC (area under the curve, area under the concentration-time curve, in $ng \cdot h \cdot l^{-1}$), oral bioavailability (the dose-normalized ratio of AUC after oral administration and AUC after intravenous administration), the so-called brain-plasma ratio (the ratio of AUC in brain tissue and AUC in plasma);

8.) no or only low blockade of the hERG channel: compounds which block the hERG channel may cause a prolongation of the QT interval and thus lead to serious disturbances of cardiac rhythm (for example so-called "torsade de pointes"). The potential of compounds to block the hERG channel can be determined by means of the displacement assay with radiolabelled dofetilide which is described in the literature (G. J. Diaz et al., *Journal of Pharmacological and Toxicological Methods*, 50 (2004), 187-199). A smaller IC_{50} in this dofetilide assay means a greater probability of potent hERG blockade. In addition, the blockade of the hERG channel can be measured by electrophysiological experiments on cells which have been transfected with the hERG channel, by so-called whole-cell patch clamping (G. J. Diaz et al., *Journal of Pharmacological and Toxicological Methods*, 50 (2004), 187-199).

It was therefore an object of the present invention to provide compounds for the treatment or prophylaxis of various vasopressin-related diseases. The compounds were intended to have a high activity and selectivity, especially a high affinity and selectivity vis-à-vis the vasopressin V1b receptor. In addition, the substance of the invention was intended to have one or more of the aforementioned advantages 1.) to 8.).

The object is achieved by compounds of the formula I



wherein

A is a ring selected from phenyl and 6-membered hetaryl containing 1 or 2 nitrogen atoms as ring members, where ring A carries one substituent R^6 and optionally one substituent R^7 ;

3

B is a ring selected from phenyl, pyridyl and quinolinyll, where ring B may carry 1, 2 or 3 substituents R⁸;

X¹ is NH, CH₂ or O;

X² is N or CH;

X³, X⁴, X⁵ and X⁶, independently of each other, are selected from —CH₂—, —O—, —S(O)_c—, —NH—, —C(O)—, —CH₂CH₂—, —CH₂O—, —OCH₂—, —S(O)_cCH₂—, —CH₂S(O)_c—, CH₂NH—, —NHCH₂—, —CH₂C(O)— and —C(O)CH₂—;

X⁷ is NH, CH₂ or O;

R¹ is selected from cyano, halogen, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R² is selected from hydrogen, cyano, halogen, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R³ and R⁴, independently of each other and independently of each occurrence, are selected from hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and NR⁹R¹⁰, and in case that R³ or R⁴ are bound to a carbon ring atom, are additionally selected from halogen; or

two non-geminal radicals R³ form together a group —(CH₂)_k—, where k is 1, 2, 3 or 4, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two non-geminal radicals R⁴ form together a group —(CH₂)_k—, where k is 1, 2, 3 or 4, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two geminal radicals R³ form together a group —(CH₂)_j—, where j is 2, 3, 4 or 5, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two geminal radicals R⁴ form together a group —(CH₂)_j—, where j is 2, 3, 4 or 5, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; with the proviso that R³ and R⁴ are not halogen, hydroxyl, C₁-C₄-alkoxy or C₁-C₄-haloalkoxy if they are bound to a carbon atom in α-position to a nitrogen ring atom;

R⁵ is selected from hydrogen, cyano, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, where the four last-mentioned radicals may be partially or fully halogenated and/or may carry one or more substituents R¹¹; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members; a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; —OR¹³; —S(O)₁R¹³; NR¹⁴R¹⁵; and —C(=O)R¹⁶;

R⁶ and R⁷, independently of each other, are selected from halogen, cyano, hydroxyl, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

each R⁸ is independently selected from halogen, cyano, hydroxyl, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

4

R⁹ and R¹⁰, independently of each other, are selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₄-alkyl, phenyl and benzyl;

each R¹¹ is independently selected from cyano, —OR¹³, —S(O)₁R¹³, NR¹⁴R¹⁵, —C(=O)R¹⁶, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and

as a substituent on a cycloalkyl ring, R¹¹ is additionally selected from C₁-C₄-alkyl and C₁-C₄-haloalkyl;

each R¹² is independently selected from halogen, hydroxyl, cyano, nitro, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfinyl, C₁-C₄-haloalkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, phenyl, phenoxy, benzyloxy, where the phenyl moiety in the three last-mentioned radicals may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy;

each R¹³ is independently selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkyl which carries one substituent R¹⁷, C₂-C₄-alkenyl, C₂-C₄-haloalkenyl, C₂-C₄-alkynyl, C₂-C₄-haloalkynyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl which may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heterocyclic ring may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy;

R¹⁴ and R¹⁵, independently of each other and independently of each occurrence, are selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl which may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heterocyclic ring may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; C₁-C₄-alkylcarbonyl and C₁-C₄-haloalkylcarbonyl;

5

each R¹⁶ is independently selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl, —OR¹³ and NR¹⁴R¹⁵;

each R¹⁷ is independently selected from cyano, hydroxyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfinyl, C₁-C₄-haloalkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, NR¹⁴R¹⁵; C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²;

a is 0, 1 or 2;

b is 0, 1 or 2;

c is 0, 1 or 2; and

l is 0, 1 or 2;

and the N-oxides, stereoisomers and pharmaceutically acceptable salts thereof, and the compound of the formula I, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope.

Accordingly, the present invention relates to compounds of the formula I (also “compounds I” hereinafter) and the N-oxides, stereoisomers and the pharmaceutically acceptable salts of the compounds I.

In another aspect, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula I or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof, or comprising at least one compound as defined above or below wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, preferably wherein at least one hydrogen atom has been replaced by a deuterium atom, in combination with at least one pharmaceutically acceptable carrier and/or auxiliary substance.

In yet another aspect, the invention relates to a compound of formula I or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof for use as a medicament.

In yet another aspect, the invention relates to a compound of formula I or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof for the treatment and/or prophylaxis of vasopressin-related diseases, especially of disorders which respond to the modulation of the vasopressin receptor, in particular of the V1b receptor.

In yet another aspect, the invention relates to the use of a compound of formula I or of an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasopressin-related diseases; especially of disorders which respond to the modulation of the vasopressin receptor, in particular of the V1b receptor.

The pharmaceutically acceptable salts of compounds of the formula I, which are also referred to as physiologically tolerated salts, are ordinarily obtainable by reacting the free base of the compounds I of the invention (i.e. of the compounds I according to structural formula I) with suitable acids. Examples of suitable acids are listed in “Fortschritte der Arzneimittelforschung”, 1966, Birkhäuser Verlag, vol. 10, pp. 224-285. These include for example hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid,

6

methanesulfonic acid, acetic acid, trifluoroacetic acid, formic acid, maleic acid and fumaric acid.

The term “stereoisomers” encompasses both optical isomers, such as enantiomers or diastereomers, the latter existing due to more than one center of chirality in the molecule, as well as geometrical isomers (cis/trans isomers; correctly speaking, these are also diastereomers). The term “stereoisomers” also encompasses conformers (to be more precise configuration isomers) which are caused by the hindered or decelerated inversion at one or more nitrogen atoms, especially ring nitrogen atoms, such as X⁷ (if this is N, of course); like the isomers described by Y. Naruse et al. in *Tetrahedron Asymmetry* 2013, 24, 169-171.

Depending on the substitution pattern, the compounds of the formula I may have one or more centers of chirality, in which case they are present as mixtures of enantiomers or diastereomers. One center of chirality is the carbon ring atom in the 3-position of the oxindole scaffold (the carbon atom which carries the group X¹—C(O)-spiro rings and ring A). The compounds of the formula I may further have axial chirality due to the spiro system. The invention provides both the pure enantiomers or diastereomers and their mixtures and the use according to the invention of the pure enantiomers or diastereomers of the compound I or its mixtures. Suitable compounds of the formula I also include all possible geometrical stereoisomers (cis/trans isomers) and mixtures thereof.

Halogen in the terms of the present invention is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine and especially fluorine or chlorine.

C₁-C₃-Alkyl is a linear or branched alkyl radical having 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl or isopropyl. C₁-C₄-Alkyl is a linear or branched alkyl radical having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl. C₁-C₆-Alkyl is a linear or branched alkyl radical having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, or 1-ethyl-2-methylpropyl.

Fluorinated alkyl is a straight-chain or branched alkyl group having from 1 to 4 (=fluorinated C₁-C₄-alkyl), in particular 1 to 3 carbon atoms (=fluorinated C₁-C₃-alkyl), more preferably 1 or 2 carbon atoms (=fluorinated C₁-C₂-alkyl), wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by fluorine atoms. Examples for fluorinated C₁-C₂-alkyl are fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like. Examples for fluorinated C₁-C₃-alkyl are, apart those mentioned above for fluorinated C₁-C₂-alkyl, 1-fluoropropyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-fluoropropyl, 2-fluoro-1-methylethyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, 2,2-difluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, 1,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-

methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl and the like. Examples for fluorinated C₁-C₄-alkyl are, apart those mentioned above for fluorinated C₁-C₃-alkyl, 1-fluorobutyl, (R)-1-fluorobutyl, (S)-1-fluorobutyl, 2-fluorobutyl, 3-fluorobutyl, 4-fluorobutyl, 1,1-difluorobutyl, 2,2-difluorobutyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, and the like.

Haloalkyl, which is also expressed as "alkyl which is partially or fully halogenated", is a straight-chain or branched alkyl group having from 1 to 6 (=C₁-C₆-haloalkyl), in particular 1 to 4 carbon atoms (=C₁-C₄-haloalkyl), wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a halogen atom. Examples for C₁-C₄-haloalkyl are, apart those mentioned above for fluorinated C₁-C₄-alkyl, chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, 3-chloropropyl, 4-chlorobutyl and the like. Examples for C₁-C₆-haloalkyl are, apart from those listed for C₁-C₄-haloalkyl, 1-fluoropentyl, 1-chloropentyl, 1-bromopentyl, 1-fluorohexyl, 1-chlorohexyl, 1-bromohexyl and the like.

C₁-C₃-Hydroxyalkyl is C₁-C₃-alkyl as defined above wherein one of the hydrogen atoms is replaced by a hydroxyl group. Examples are hydroxymethyl, 1- and 2-hydroxyethyl, 1-, 2- and 3-hydroxy-n-propyl, 1-(hydroxymethyl)-ethyl and the like.

The term "alkenyl" as used herein refers to monounsaturated straight-chain or branched hydrocarbon radicals having 2 to 3 ("C₂-C₃-alkenyl"), 2 to 4 ("C₂-C₄-alkenyl") or 2 to 6 ("C₂-C₆-alkenyl") carbon atoms and a double bond in any position. Examples for C₂-C₃-alkenyl are ethenyl, 1-propenyl, 2-propenyl or 1-methylethenyl. Examples for C₂-C₄-alkenyl are ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl or 2-methyl-2-propenyl. Examples for C₂-C₆-alkenyl are ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl, 1-ethyl-2-methyl-2-propenyl and the like.

The term "haloalkenyl" as used herein, which is also expressed as "alkenyl which is partially or fully haloge-

nated", refers to unsaturated straight-chain or branched hydrocarbon radicals having 2 to 3 ("C₂-C₃-haloalkenyl"), 2 to 4 ("C₂-C₄-haloalkenyl") or 2 to 6 ("C₂-C₆-haloalkenyl") carbon atoms and a double bond in any position (as mentioned above), where some or all of the hydrogen atoms in these groups are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine, for example chlorovinyl, chloroallyl and the like.

The term "alkynyl" as used herein refers to straight-chain or branched hydrocarbon groups having 2 to 3 ("C₂-C₃-alkynyl"), 2 to 4 ("C₂-C₄-alkynyl") or 2 to 6 ("C₂-C₆-alkynyl") carbon atoms and one or two triple bonds in any position. Examples for C₂-C₃-alkynyl are ethynyl, 1-propynyl or 2-propynyl. Examples for C₂-C₄-alkynyl are ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-methyl-2-propynyl and the like. Examples for C₂-C₆-alkynyl are ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-methyl-2-propynyl, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-methyl-2-butyne, 1-methyl-3-butyne, 2-methyl-3-butyne, 3-methyl-1-butyne, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentyne, 1-methyl-3-pentyne, 1-methyl-4-pentyne, 2-methyl-3-pentyne, 2-methyl-4-pentyne, 3-methyl-1-pentyne, 3-methyl-4-pentyne, 4-methyl-1-pentyne, 4-methyl-2-pentyne, 1,1-dimethyl-2-butyne, 1,1-dimethyl-3-butyne, 1,2-dimethyl-3-butyne, 2,2-dimethyl-3-butyne, 3,3-dimethyl-1-butyne, 1-ethyl-2-butyne, 1-ethyl-3-butyne, 2-ethyl-3-butyne, 1-ethyl-1-methyl-2-propynyl and the like.

The term "haloalkynyl" as used herein, which is also expressed as "alkynyl which is partially or fully halogenated", refers to unsaturated straight-chain or branched hydrocarbon radicals having 2 to 3 ("C₂-C₃-haloalkynyl"), 2 to 4 ("C₂-C₄-haloalkynyl") or 2 to 6 ("C₂-C₆-haloalkynyl") carbon atoms and one or two triple bonds in any position (as mentioned above), where some or all of the hydrogen atoms in these groups are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine.

C₃-C₇-Cycloalkyl is a monocyclic saturated hydrocarbon radical having 3 to 7, in particular 3 to 6 ("C₃-C₆-cycloalkyl") or 3 to 5 ("C₃-C₅-cycloalkyl") or 3 to 4 ("C₃-C₄-cycloalkyl") carbon atoms. Examples of C₃-C₄-cycloalkyl comprise cyclopropyl and cyclobutyl. Examples of C₃-C₅-cycloalkyl comprise cyclopropyl, cyclobutyl and cyclopentyl. Examples of C₃-C₆-cycloalkyl comprise cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of C₃-C₇-cycloalkyl comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Fluorinated C₃-C₇-cycloalkyl is a monocyclic saturated hydrocarbon radical having 3 to 7, in particular 3 to 6 ("fluorinated C₃-C₆-cycloalkyl") or 3 to 5 ("fluorinated C₃-C₅-cycloalkyl") or 3 to 4 ("fluorinated C₃-C₄-cycloalkyl") carbon ring members (as mentioned above) in which some or all of the hydrogen atoms are replaced by fluorine atoms. Examples for fluorinated C₃-C₄-cycloalkyl are 1-fluorocyclopropyl, 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, 1-fluorocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl and the like. Examples for fluorinated C₃-C₅-cycloalkyl are additionally 1-fluorocyclopentyl, 2-fluorocyclopentyl, 3-fluorocyclopentyl, 2,2-difluorocyclopentyl, 3,3-difluorocyclopentyl, and the like. Examples for fluorinated C₃-C₆-cycloalkyl are additionally 1-fluorocyclohexyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl, 4,4-difluorocyclohexyl, and the like. Examples for fluorinated

C₃-C₇-cycloalkyl are additionally 1-fluorocycloheptyl, 2-fluorocycloheptyl, 3-fluorocycloheptyl, 4-fluorocycloheptyl, 2,2-difluorocycloheptyl, 3,3-difluorocycloheptyl, 4,4-difluorocycloheptyl, and the like.

C₃-C₇-Halocycloalkyl is a monocyclic saturated hydrocarbon radical having 3 to 7, in particular 3 to 6 ("C₃-C₆-halocycloalkyl") or 3 to 5 ("C₃-C₅-halocycloalkyl") or 3 to 4 ("C₃-C₄-halocycloalkyl") carbon ring members (as mentioned above) in which some or all of the hydrogen atoms are replaced by halogen atoms as mentioned above, in particular fluorine, chlorine and bromine.

The term "C₃-C₆-cycloalkyl-C₁-C₄-alkyl" which is bound to the remainder of the molecule via a C₁-C₄-alkyl group, as defined above. Examples for C₃-C₆-cycloalkyl-C₁-C₄-alkyl are cyclopropylmethyl, 1-cyclopropyl-1-ethyl, 1-cyclopropyl-2-ethyl, 1-cyclopropyl-1-propyl, 1-cyclopropyl-2-propyl, 2-cyclopropyl-1-propyl, 2-cyclopropyl-2-propyl, 1-cyclopropyl-3-propyl, cyclobutylmethyl, 1-cyclobutyl-1-ethyl, 1-cyclobutyl-2-ethyl, 1-cyclobutyl-1-propyl, 1-cyclobutyl-2-propyl, 2-cyclobutyl-1-propyl, 2-cyclobutyl-2-propyl, 1-cyclobutyl-3-propyl, cyclopentylmethyl, 1-cyclopentyl-1-ethyl, 1-cyclopentyl-2-ethyl, 1-cyclopentyl-1-propyl, 1-cyclopentyl-2-propyl, 2-cyclopentyl-1-propyl, 2-cyclopentyl-2-propyl, 1-cyclopentyl-3-propyl, cyclohexylmethyl, 1-cyclohexyl-1-ethyl, 1-cyclohexyl-2-ethyl, 1-cyclohexyl-1-propyl, 1-cyclohexyl-2-propyl, 2-cyclohexyl-1-propyl, 2-cyclohexyl-2-propyl and 1-cyclohexyl-3-propyl.

C₃-C₆-Cycloalkylmethyl is for example cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

C₁-C₃-Alkoxy is a linear or branched alkyl radical linked via an oxygen atom and having 1 to 3 carbon atoms. Examples are methoxy, ethoxy, n-propoxy and isopropoxy. C₁-C₄-Alkoxy is a linear or branched alkyl radical linked via an oxygen atom and having 1 to 4 carbon atoms. Examples are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy and tert-butoxy.

C₁-C₄-Haloalkoxy is C₁-C₄-alkoxy as defined above wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a halogen atom. Preferably, C₁-C₄-haloalkoxy is fluorinated C₁-C₄-alkoxy. This is a straight-chain or branched alkoxy group having from 1 to 4, in particular 1 to 3 carbon atoms (=fluorinated C₁-C₃-alkoxy), more preferably 1 or 2 carbon atoms (=fluorinated C₁-C₂-alkoxy), wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by fluorine atoms, such as in fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-fluoroethoxy, (R)-1-fluoroethoxy, (S)-1-fluoroethoxy, 2-fluoroethoxy, 1,1-difluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 1-fluoropropoxy, (R)-1-fluoropropoxy, (S)-1-fluoropropoxy, 2-fluoropropoxy, 3-fluoropropoxy, 1,1-difluoropropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, 2-fluoro-1-methylethoxy, (R)-2-fluoro-1-methylethoxy, (S)-2-fluoro-1-methylethoxy, 2,2-difluoro-1-methylethoxy, (R)-2,2-difluoro-1-methylethoxy, (S)-2,2-difluoro-1-methylethoxy, 1,2-difluoro-1-methylethoxy, (R)-1,2-difluoro-1-methylethoxy, (S)-1,2-difluoro-1-methylethoxy, 2,2,2-trifluoro-1-methylethoxy, (R)-2,2,2-trifluoro-1-methylethoxy, (S)-2,2,2-trifluoro-1-methylethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, (R)-1-fluorobutoxy, (S)-1-fluorobutoxy, 2-fluorobutoxy, 3-fluorobutoxy, 4-fluorobutoxy, 1,1-difluorobutoxy, 2,2-difluorobutoxy, 3,3-difluorobutoxy, 4,4-difluorobutoxy, 4,4,4-trifluorobutoxy, etc.

C₁-C₄-Alkylthio is a C₁-C₄-alkyl group, as defined above, attached via a sulfur atom. Examples are methylthio, ethylthio, n-propylthio, 1-methylethylthio (isopropylthio), butyl-

thio, 1-methylpropylthio (sec-butylthio), 2-methylpropylthio (isobutylthio) or 1,1-dimethylethylthio (tert-butylthio).

C₁-C₄-Haloalkylthio is a C₁-C₄-haloalkyl group, as defined above, attached via a sulfur atom. Examples are SCH₂F, SCHF₂, SCF₃, SCH₂Cl, SCHCl₂, SCl₃, chlorofluoromethylthio, dichlorofluoromethylthio, chlorodifluoromethylthio, 2-fluoroethylthio, 2-chloroethylthio, 2-bromoethylthio, 2-iodoethylthio, 2,2-difluoroethylthio, 2,2,2-trifluoroethylthio, 2-chloro-2-fluoroethylthio, 2-chloro-2,2-difluoroethylthio, 2,2-dichloro-2-fluoroethylthio, 2,2,2-trichloroethylthio, SC₂F₅, 2-fluoropropylthio, 3-fluoropropylthio, 2,2-difluoropropylthio, 2,3-difluoropropylthio, 2-chloropropylthio, 3-chloropropylthio, 2,3-dichloropropylthio, 2-bromopropylthio, 3-bromopropylthio, 3,3,3-trifluoropropylthio, 3,3,3-trichloropropylthio, SCH₂-C₂F₅, SCF₂-C₂F₅, 1-(CH₂F)-2-fluoroethylthio, 1-(CH₂Cl)-2-chloroethylthio, 1-(CH₂Br)-2-bromoethylthio, 4-fluorobutylthio, 4-chlorobutylthio, 4-bromobutylthio or nonafluorobutylthio.

C₁-C₄-Alkylsulfinyl is a C₁-C₄-alkyl group, as defined above, attached via a sulfinyl [S(O)]group. Examples are methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, 1-methylethylsulfinyl (isopropylsulfinyl), butylsulfinyl, 1-methylpropylsulfinyl (sec-butylsulfinyl), 2-methylpropylsulfinyl (isobutylsulfinyl) or 1,1-dimethylethylsulfinyl (tert-butylsulfinyl).

C₁-C₄-Haloalkylsulfinyl is a C₁-C₄-haloalkyl group, as defined above, attached via a sulfinyl [S(O)]group. Examples are S(O)CH₂F, S(O)CHF₂, S(O)CF₃, S(O)CH₂Cl, S(O)CHCl₂, S(O)CCl₃, chlorofluoromethylsulfinyl, dichlorofluoromethylsulfinyl, chlorodifluoromethylsulfinyl, 2-fluoroethylsulfinyl, 2-chloroethylsulfinyl, 2-bromoethylsulfinyl, 2-iodoethylsulfinyl, 2,2-difluoroethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2-chloro-2-fluoroethylsulfinyl, 2-chloro-2,2-difluoroethylsulfinyl, 2,2-dichloro-2-fluoroethylsulfinyl, 2,2,2-trichloroethylsulfinyl, S(O)C₂F₅, 2-fluoropropylsulfinyl, 3-fluoropropylsulfinyl, 2,2-difluoropropylsulfinyl, 2,3-difluoropropylsulfinyl, 2-chloropropylsulfinyl, 3-chloropropylsulfinyl, 2,3-dichloropropylsulfinyl, 2-bromopropylsulfinyl, 3-bromopropylsulfinyl, 3,3,3-trifluoropropylsulfinyl, 3,3,3-trichloropropylsulfinyl, S(O)CH₂-C₂F₅, S(O)CF₂-C₂F₅, 1-(CH₂F)-2-fluoroethylsulfinyl, 1-(CH₂Cl)-2-chloroethylsulfinyl, 1-(CH₂Br)-2-bromoethylsulfinyl, 4-fluorobutylsulfinyl, 4-chlorobutylsulfinyl, 4-bromobutylsulfinyl or nonafluorobutylsulfinyl.

C₁-C₄-Alkylsulfonyl is a C₁-C₄-alkyl group, as defined above, attached via a sulfonyl [S(O)₂]group. Examples are methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, 1-methylethylsulfonyl (isopropylsulfonyl), butylsulfonyl, 1-methylpropylsulfonyl (sec-butylsulfonyl), 2-methylpropylsulfonyl (isobutylsulfonyl) or 1,1-dimethylethylsulfonyl (tert-butylsulfonyl).

C₁-C₄-Haloalkylsulfonyl is a C₁-C₄-haloalkyl group, as defined above, attached via a sulfonyl [S(O)₂]group. Examples are S(O)₂CH₂F, S(O)₂CHF₂, S(O)₂CF₃, S(O)₂CH₂Cl, S(O)₂CHCl₂, S(O)₂CCl₃, chlorofluoromethylsulfonyl, dichlorofluoromethylsulfonyl, chlorodifluoromethylsulfonyl, 2-fluoroethylsulfonyl, 2-chloroethylsulfonyl, 2-bromoethylsulfonyl, 2-iodoethylsulfonyl, 2,2-difluoroethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2-chloro-2-fluoroethylsulfonyl, 2-chloro-2,2-difluoroethylsulfonyl, 2,2-dichloro-2-fluoroethylsulfonyl, 2,2,2-trichloroethylsulfonyl, S(O)₂C₂F₅, 2-fluoropropylsulfonyl, 3-fluoropropylsulfonyl, 2,2-difluoropropylsulfonyl, 2,3-difluoropropylsulfonyl, 2-chloropropylsulfonyl, 3-chloropropylsulfonyl, 2,3-dichloropropylsulfonyl, 2-bromopropylsulfonyl, 3-bromopropylsulfonyl, 3,3,3-trifluoropropylsulfonyl, 3,3,3-trichloropropylsulfonyl, S(O)₂CH₂-C₂F₅, S(O)₂CF₂-C₂F₅,

11

1-(CH₂F)-2-fluoroethylsulfonyl, 1-(CH₂Cl)-2-chloroethylsulfonyl, 1-(CH₂Br)-2-bromoethylsulfonyl, 4-fluorobutylsulfonyl, 4-chlorobutylsulfonyl, 4-bromobutylsulfonyl or nonafluorobutylsulfonyl.

C₁-C₄-Alkylcarbonyl is a C₁-C₄-alkyl group, as defined above, attached via a carbonyl [C(=O)]group. Examples are acetyl (methylcarbonyl), propionyl (ethylcarbonyl), propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl and the like.

C₁-C₄-Haloalkylcarbonyl is a C₁-C₄-haloalkyl group, as defined above, attached via a carbonyl [C(=O)]group. Examples are trifluoromethylcarbonyl, 2,2,2-trifluoroethylcarbonyl and the like.

Examples for "6-membered hetaryl containing 1 or 2 nitrogen atoms as ring members" are pyridyl, such as pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, pyridazinyl, such as pyridazin-3-yl or pyridazin-4-yl, pyrimidinyl, such as pyrimidin-2-yl, pyrimidin-4-yl or pyrimidin-5-yl, and pyrazinyl.

The term "3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members" denotes a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximum unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂, as ring members.

Unsaturated rings contain at least one C—C and/or C—N and/or N—N double bond(s). Maximally unsaturated rings contain as many conjugated C—C and/or C—N and/or N—N double bonds as allowed by the ring size. Maximally unsaturated 5- or 6-membered heterocyclic rings are aromatic. Partially unsaturated rings contain less C—C and/or C—N and/or N—N double bonds than allowed by the ring size. The heterocyclic ring may be attached to the remainder of the molecule via a carbon ring member or via a nitrogen ring member. As a matter of course, the heterocyclic ring contains at least one carbon ring atom. If the ring contains more than one O ring atom, these are not adjacent.

The term "3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximum unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂, as ring members" [wherein "maximum unsaturated" includes also "aromatic"] as used herein denotes monocyclic radicals, the monocyclic radicals being saturated, partially unsaturated or maximum unsaturated (including aromatic). 7-membered rings cannot be aromatic; they are homoaromatic if maximally unsaturated (3 double bonds).

Examples of a 3-, 4-, 5-, 6- or 7-membered saturated heterocyclic ring include: Oxiranyl, thiiranyl, aziridinyl, oxetanyl, thietanyl, azetidiny, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrazolidin-1-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, oxazolidin-2-yl, oxazolidin-3-yl, oxazolidin-4-yl, oxazolidin-5-yl, isoxazolidin-2-yl, isoxazolidin-3-yl, isoxazolidin-4-yl, isoxazolidin-5-yl, thiazolidin-2-yl, thiazolidin-3-yl, thiazolidin-4-yl, thiazolidin-5-yl, isothiazolidin-2-yl, isothiazolidin-3-yl, isothiazolidin-4-yl, isothiazolidin-5-yl, 1,2,4-oxadiazolidin-3-yl, 1,2,4-oxadiazolidin-5-yl, 1,2,4-thiadiazolidin-3-yl, 1,2,4-thiadiazolidin-5-yl, 1,2,4-triazolidin-3-yl, 1,3,4-oxadiazolidin-2-yl, 1,3,4-thiadiazolidin-2-yl, 1,3,4-triazolidin-1-yl, 1,3,4-triazolidin-2-yl, 2-tetrahydropyran-4-yl, 4-tetrahydropyran-1-yl, 1,3-dioxan-5-yl, 1,4-dioxan-2-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, hexahydropyridazin-3-yl, hexahydropyridazin-4-yl, hexahy-

12

dropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl, piperazin-1-yl, piperazin-2-yl, 1,3,5-hexahydrotriazin-1-yl, 1,3,5-hexahydrotriazin-2-yl and 1,2,4-hexahydrotriazin-3-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, 1-oxothiomorpholin-2-yl, 1-oxothiomorpholin-3-yl, 1-oxothiomorpholin-4-yl, 1,1-dioxothiomorpholin-2-yl, 1,1-dioxothiomorpholin-3-yl, 1,1-dioxothiomorpholin-4-yl, azepan-1-, -2-, -3- or -4-yl, oxepan 2-, -3-, -4- or -5-yl, hexahydro-1,3-diazepinyl, hexahydro-1,4-diazepinyl, hexahydro-1,3-oxazepinyl, hexahydro-1,4-oxazepinyl, hexahydro-1,3-dioxepinyl, hexahydro-1,4-dioxepinyl and the like.

Examples of a 3-, 4-, 5-, 6- or 7-membered partially unsaturated heterocyclic ring include: 2,3-dihydrofur-2-yl, 2,3-dihydrofur-3-yl, 2,4-dihydrofur-2-yl, 2,4-dihydrofur-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,4-dihydrothien-2-yl, 2,4-dihydrothien-3-yl, 2-pyrrolin-2-yl, 2-pyrrolin-3-yl, 3-pyrrolin-2-yl, 3-pyrrolin-3-yl, 2-isoxazolin-3-yl, 3-isoxazolin-3-yl, 4-isoxazolin-3-yl, 2-isoxazolin-4-yl, 3-isoxazolin-4-yl, 4-isoxazolin-4-yl, 2-isoxazolin-5-yl, 3-isoxazolin-5-yl, 4-isoxazolin-5-yl, 2-isothiazolin-3-yl, 3-isothiazolin-3-yl, 4-isothiazolin-3-yl, 2-isothiazolin-4-yl, 3-isothiazolin-4-yl, 4-isothiazolin-4-yl, 2-isothiazolin-5-yl, 3-isothiazolin-5-yl, 4-isothiazolin-5-yl, 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-2-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl, 3,4-dihydropyrazol-1-yl, 3,4-dihydropyrazol-3-yl, 3,4-dihydropyrazol-4-yl, 3,4-dihydropyrazol-5-yl, 4,5-dihydropyrazol-1-yl, 4,5-dihydropyrazol-3-yl, 4,5-dihydropyrazol-4-yl, 4,5-dihydropyrazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-dihydrooxazol-3-yl, 2,3-dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 3,4-dihydrooxazol-2-yl, 3,4-dihydrooxazol-3-yl, 3,4-dihydrooxazol-4-yl, 3,4-dihydrooxazol-5-yl, 3,4-dihydrooxazol-2-yl, 3,4-dihydrooxazol-3-yl, 3,4-dihydrooxazol-4-yl, 2-, 3-, 4-, 5- or 6-di- or tetrahydropyridinyl, 3-di- or tetrahydropyridazinyl, 4-di- or tetrahydropyridazinyl, 2-di- or tetrahydropyrimidinyl, 4-di- or tetrahydropyrimidinyl, 5-di- or tetrahydropyrimidinyl, di- or tetrahydropyrazinyl, 1,3,5-di- or tetrahydrotriazin-2-yl, 1,2,4-di- or tetrahydrotriazin-3-yl, 2,3,4,5-tetrahydro[1H]azepin-1-, -2-, -3-, -4-, -5-, -6- or -7-yl, 3,4,5,6-tetrahydro[2H]azepin-2-, -3-, -4-, -5-, -6- or -7-yl, 2,3,4,7-tetrahydro[1H]azepin-1-, -2-, -3-, -4-, -5-, -6- or -7-yl, 2,3,6,7-tetrahydro[1H]azepin-1-, -2-, -3-, -4-, -5-, -6- or -7-yl, tetrahydrooxepinyl, such as 2,3,4,5-tetrahydro[1H]oxepin-2-, -3-, -4-, -5-, -6- or -7-yl, 2,3,4,7-tetrahydro[1H]oxepin-2-, -3-, -4-, -5-, -6- or -7-yl, 2,3,6,7-tetrahydro[1H]oxepin-2-, -3-, -4-, -5-, -6- or -7-yl, tetrahydro-1,3-diazepinyl, tetrahydro-1,4-diazepinyl, tetrahydro-1,3-oxazepinyl, tetrahydro-1,4-oxazepinyl, tetrahydro-1,3-dioxepinyl and tetrahydro-1,4-dioxepinyl.

Examples for a 3-, 4-, 5-, 6- or 7-membered maximally unsaturated (including aromatic) heterocyclic ring are 5- or 6-membered heteroaromatic rings, such as 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1,3,4-triazol-1-yl, 1,3,4-triazol-2-yl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 1-oxypyridin-2-yl, 1-oxypyridin-3-yl, 1-oxypyridin-4-yl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl and 2-pyrazinyl, and also homoaromatic radicals, such as 1H-azepine, 1H-[1,3]-diazepine and 1H-[1,4]-diazepine.

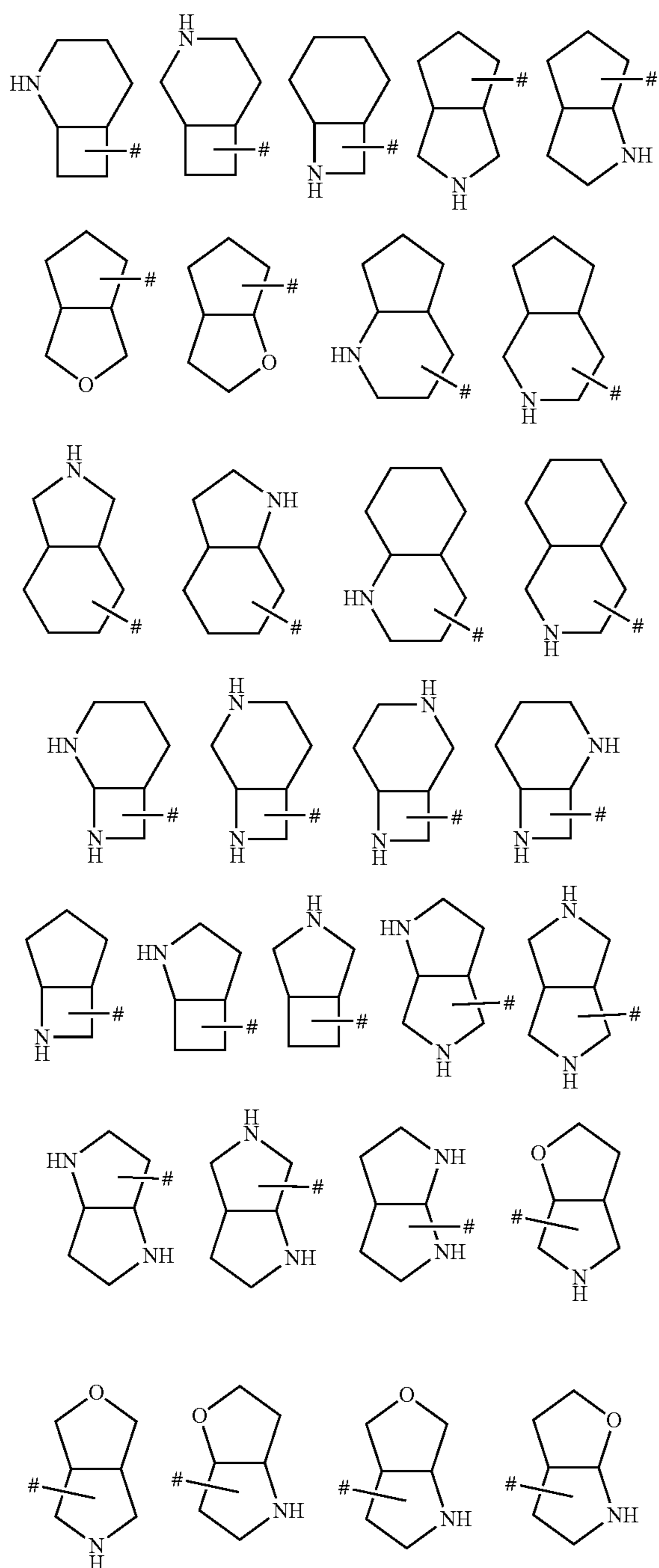
In the present invention, the "heterobicyclic rings" contain two rings which have at least one ring atom in common.

13

At least one of the two rings contains a heteroatom or heteroatom group selected from N, O, S, NO, SO and SO₂ as ring member. The term comprises condensed (fused) ring systems, in which the two rings have two neighboring ring atoms in common, as well as spiro systems, in which the rings have only one ring atom in common, and bridged systems with at least three ring atoms in common.

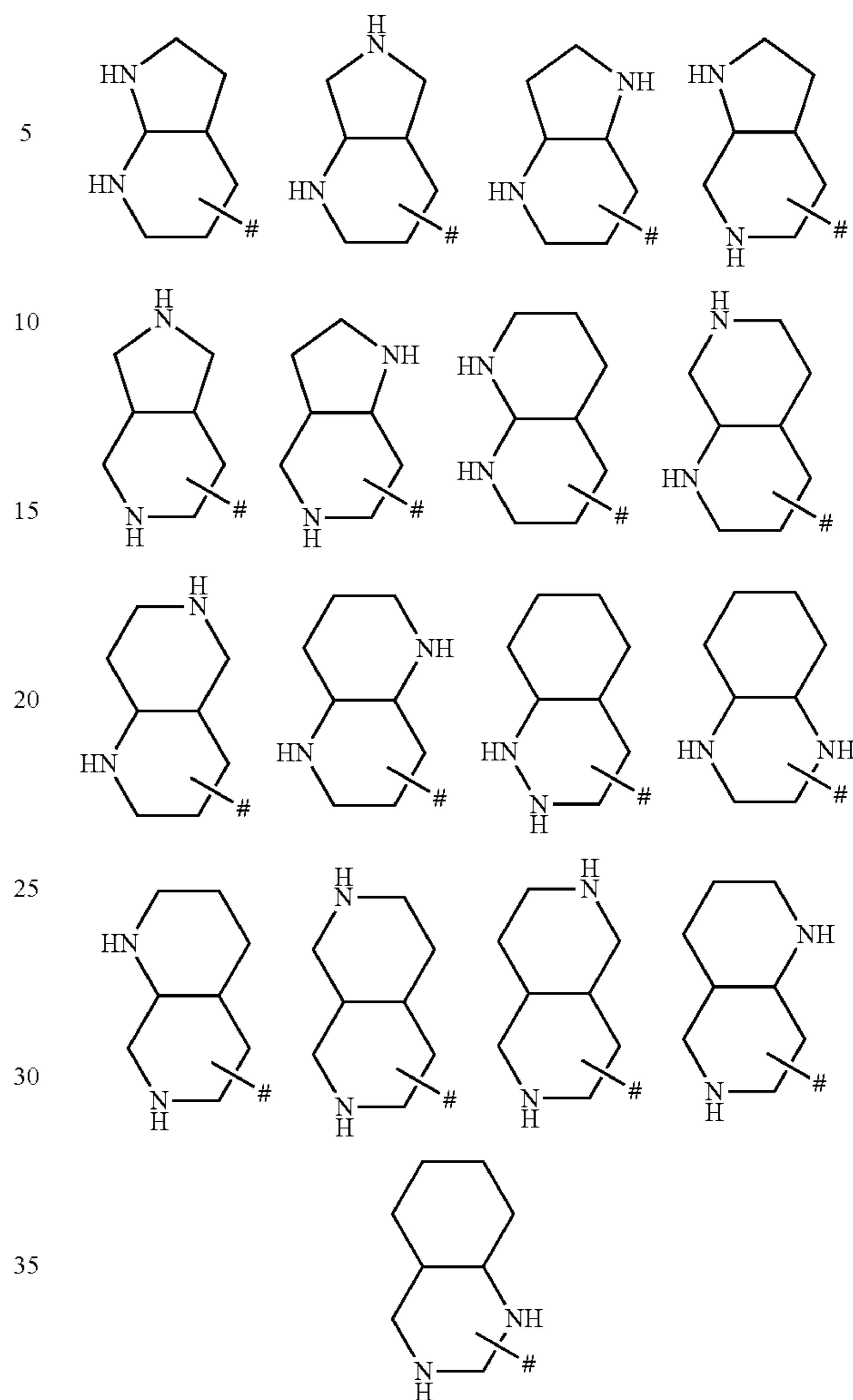
Examples for Fused Systems:

Examples for a 7-, 8-, 9- or 10-membered saturated heterobicyclic ring containing 1, 2 or 3 (or 4) heteroatoms or heteroatom groups selected from N, O, S, NO, SO and SO₂, as ring members are:

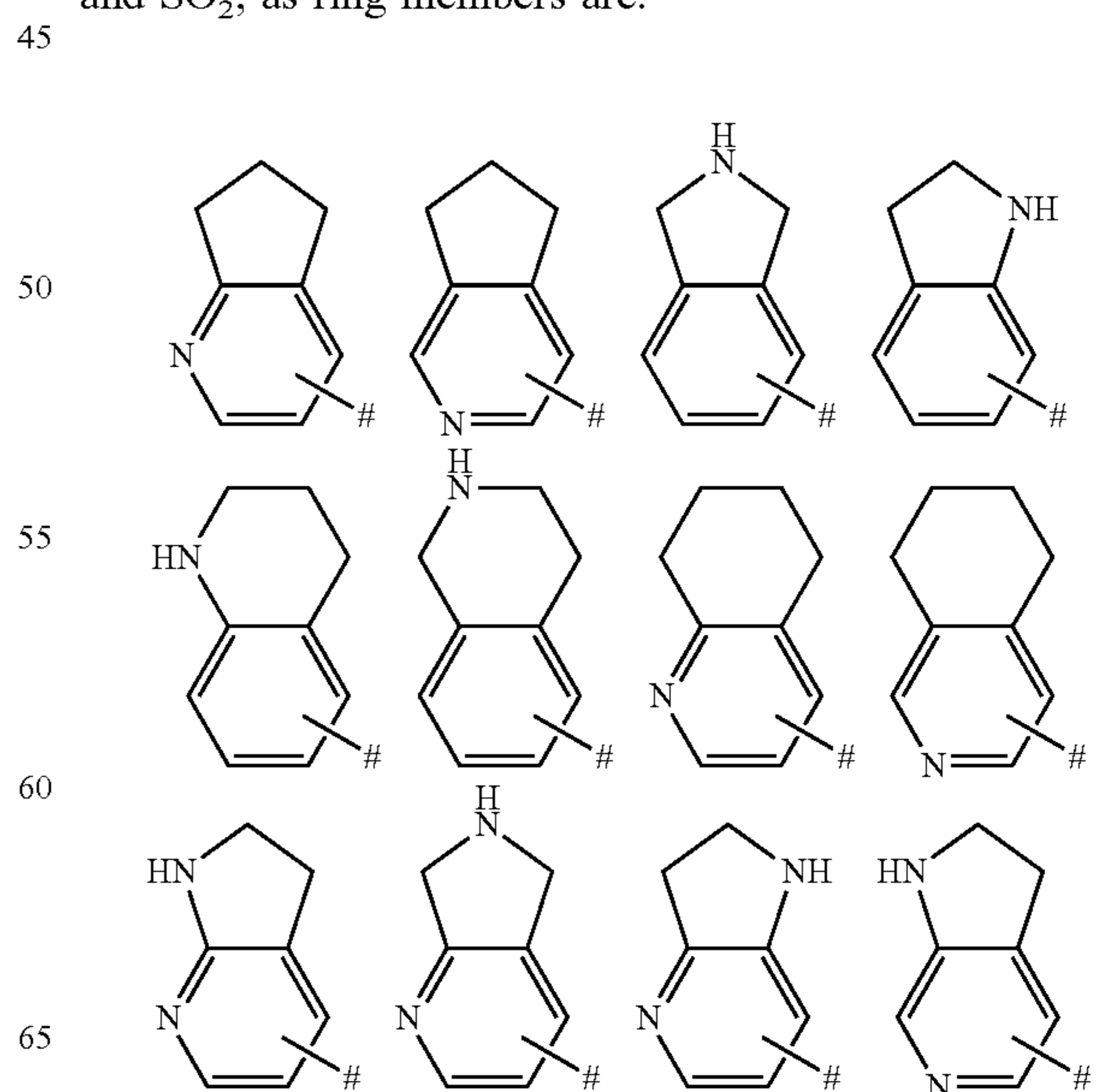


14

-continued

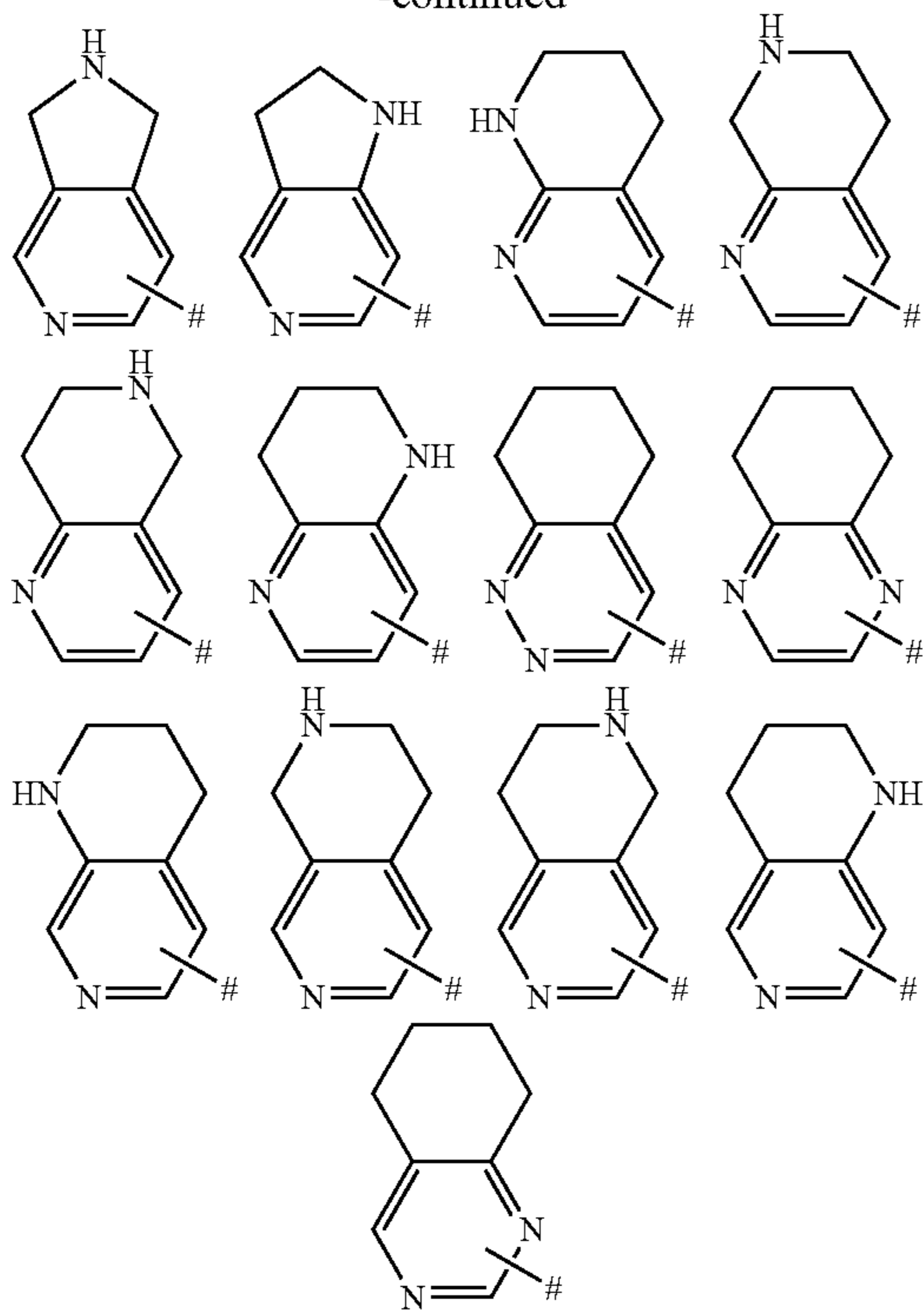


Examples for a 8-, 9- or 10-membered partially unsaturated heterobicyclic ring containing 1, 2 or 3 (or 4) heteroatoms or heteroatom groups selected from N, O, S, NO, SO and SO₂, as ring members are:

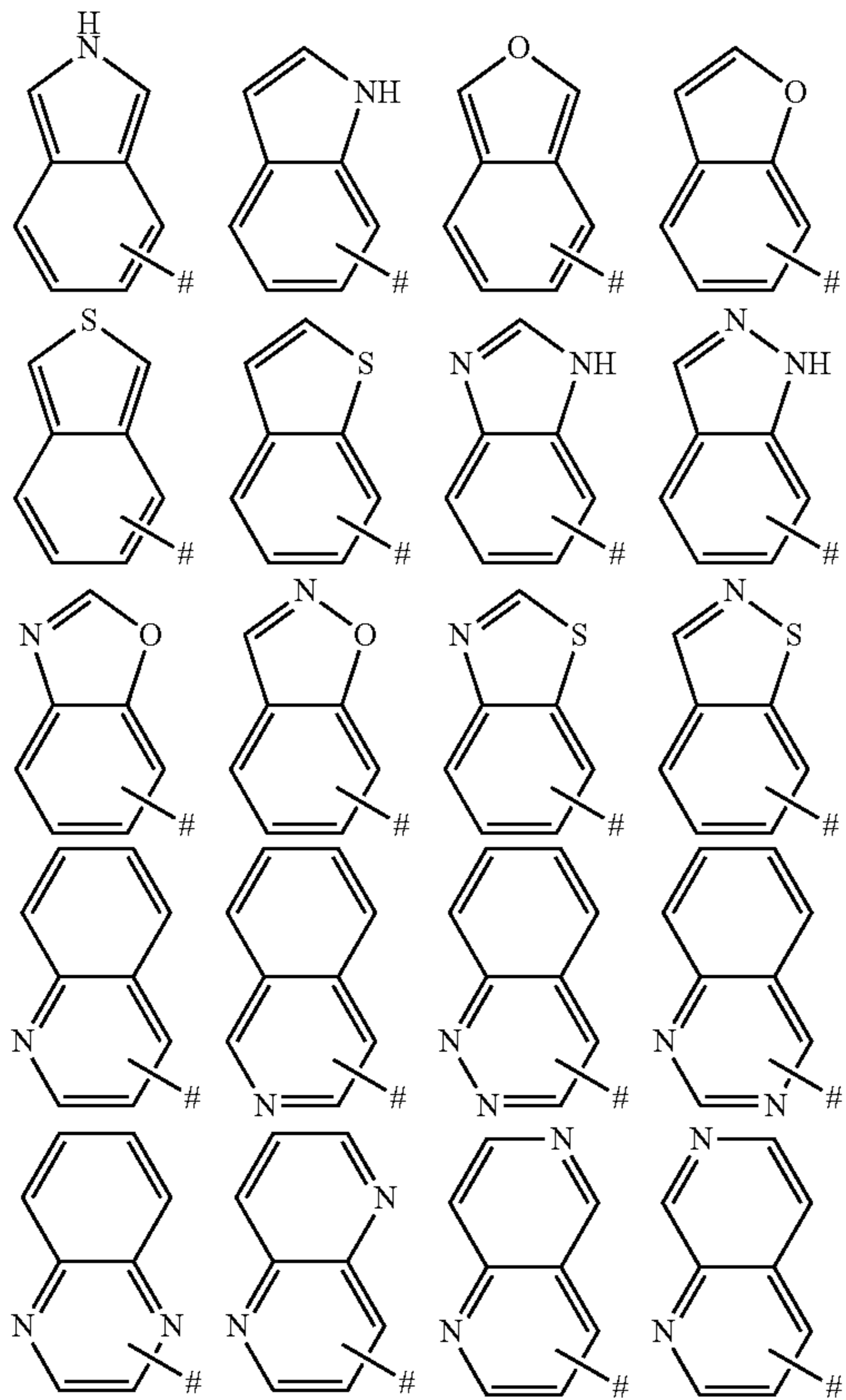


15

-continued

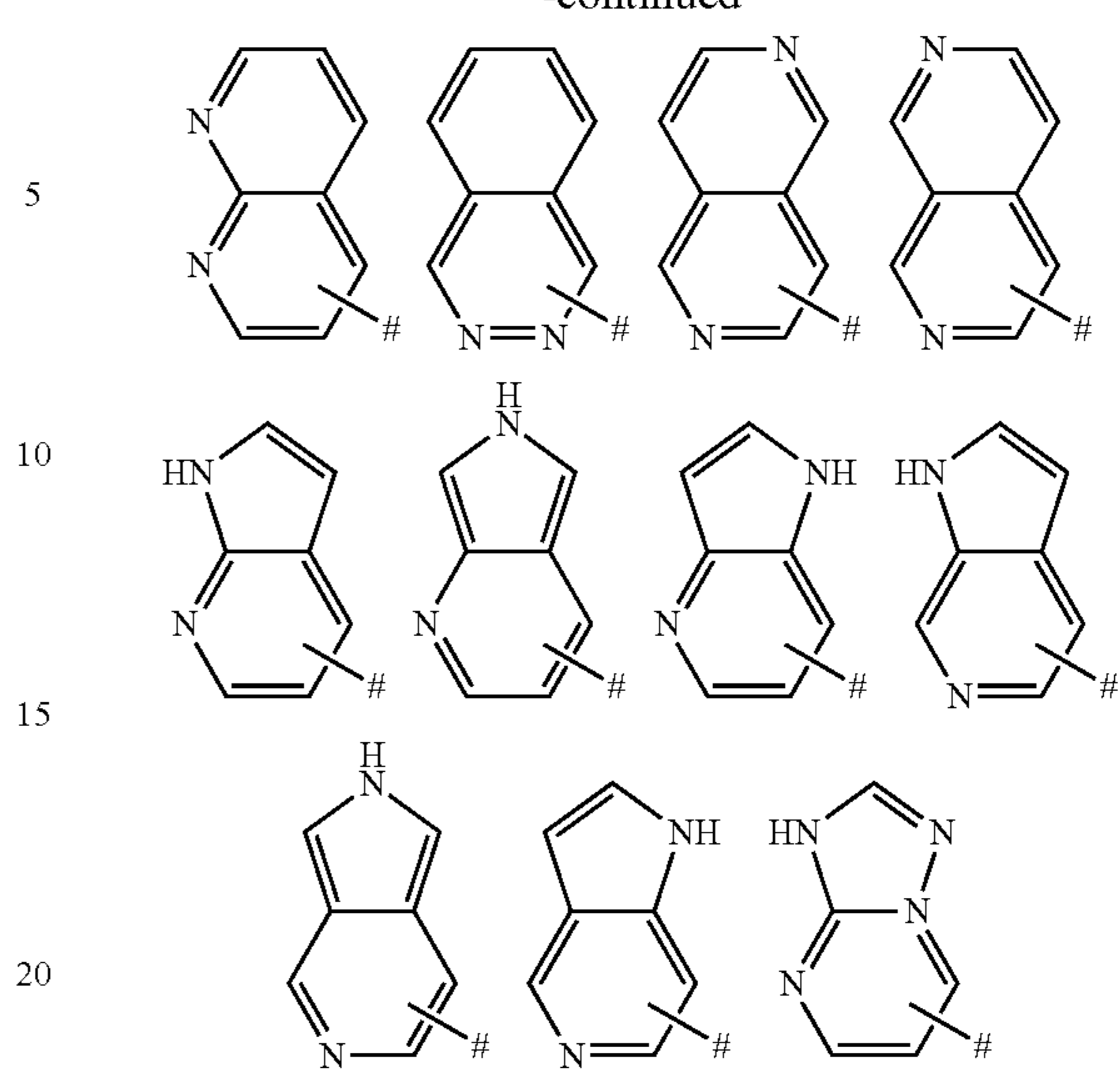


Examples for a 8-, 9- or 10-membered maximally unsaturated heterobicyclic ring containing 1, 2 or 3 (or 4) heteroatoms or heteroatom groups selected from N, O, S, NO, SO and SO₂, as ring members are:

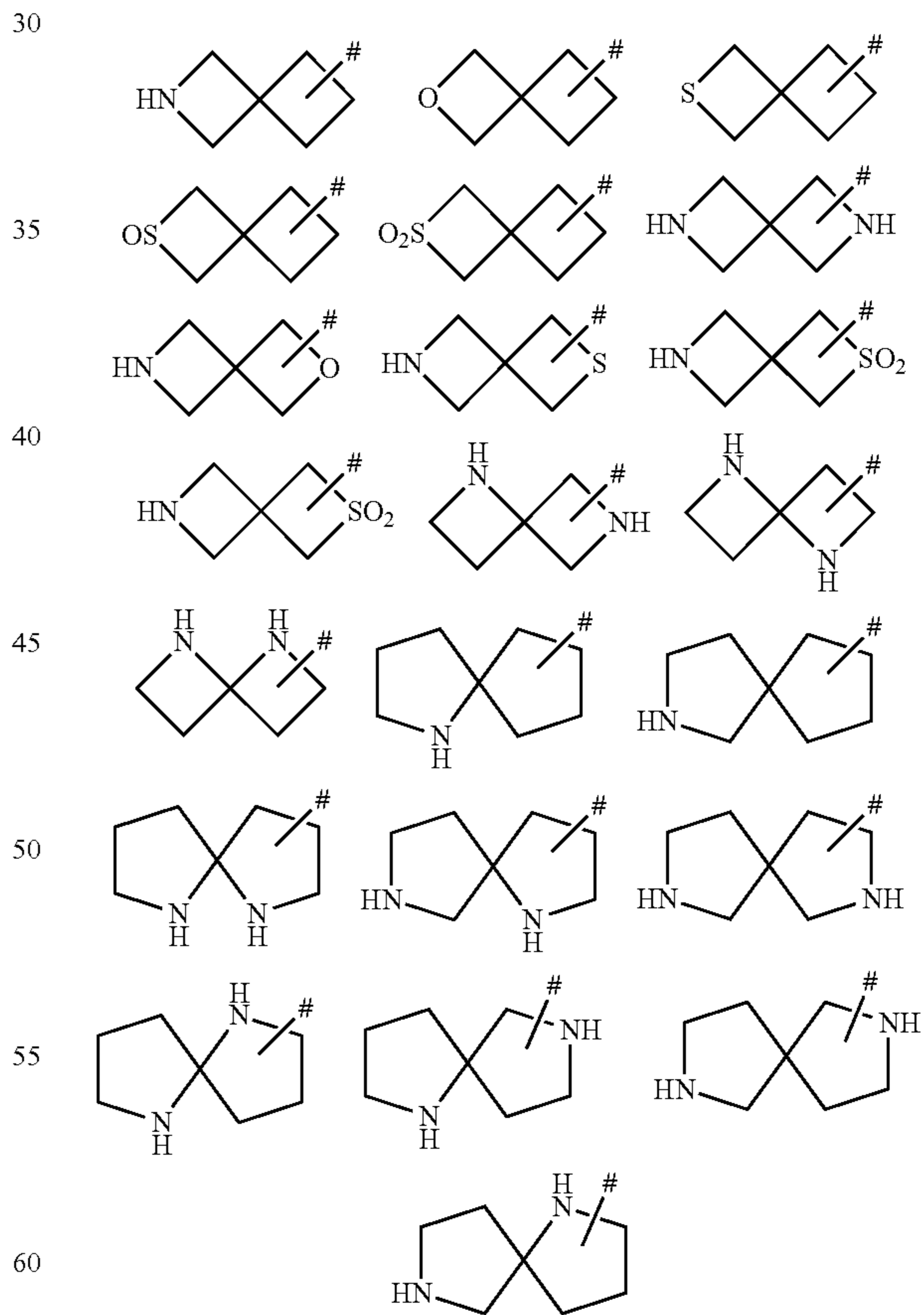


16

-continued

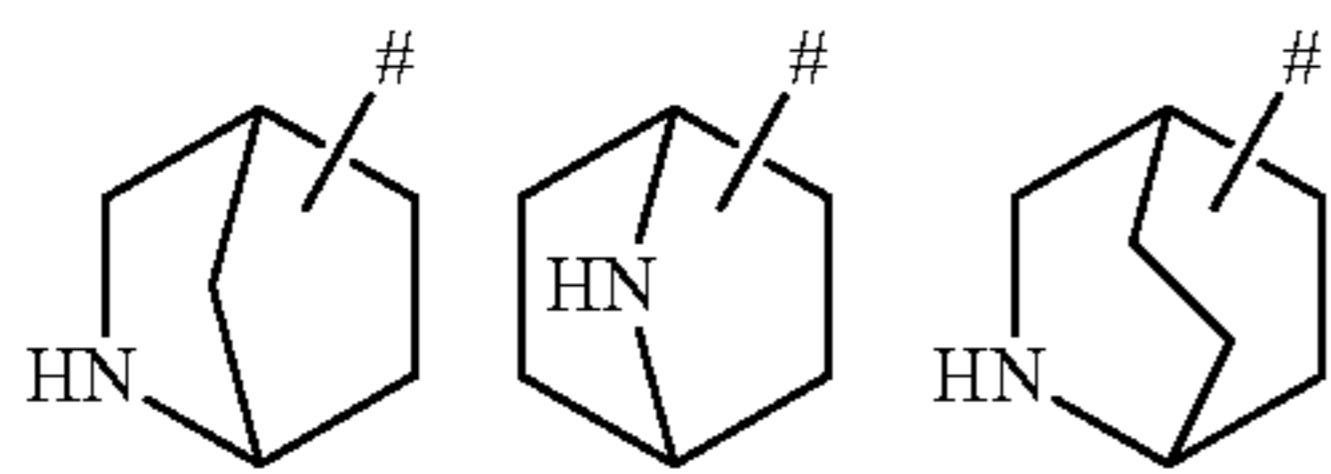


Examples for spiro-bound 7-, 8-, 9- or 10-membered heterobicyclic rings containing 1, 2 or 3 (or 4) heteroatoms or heteroatom groups selected from N, O, S, NO, SO and SO₂, as ring members are



Examples for bridged 7-, 8-, 9- or 10-membered heterobicyclic rings containing 1, 2 or 3 (or 4) heteroatoms or heteroatom groups selected from N, O, S, NO, SO and SO₂, as ring members are

17



and the like.

In the above structures # denotes the attachment point to the remainder of the molecule. The attachment point is not restricted to the ring on which is shown, but can be on either of the fused rings, and may be on a carbon or on a nitrogen ring atom. If the rings carry one or more substituents, these may be bound to carbon and/or to nitrogen ring atoms.

The compounds of the invention of the formula I and their N-oxides, stereoisomers and pharmacologically acceptable salts may also be present in the form of solvates or hydrates. Solvates mean in the context of the present invention crystalline forms of the compounds I or of their pharmaceutically acceptable salts which comprise solvent molecules incorporated in the crystal lattice. The solvent molecules are preferably incorporated in stoichiometric ratios. Hydrates are a specific form of solvates; the solvent in this case being water.

The statements made hereinafter concerning suitable and preferred features of the invention, especially concerning the radicals A, B, X¹, X², X³, X⁴, X⁵, X⁶, X⁷, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, a, b, c, k, l, m, n, o and p in the compound I, but also concerning the features of the process of the invention and of the use according to the invention apply both taken on their own as well as preferably in any possible combination with one another.

The compounds I are preferably provided in the form of the free base (i.e. according to structural formula I) or in the form of their acid addition salts.

As a matter of course, each radical R³, if present, replaces a hydrogen atom of the ring members X², X³ and/or X⁴, e.g. the hydrogen atom in X² if this is CH or the hydrogen atom(s) in the CH₂ or NH moieties of X³ and/or X⁴.

Alike, each radical R⁴, if present, as well as the mandatory radical R⁵ replace a hydrogen atom of the ring members X⁵, X⁶ and/or X⁷, e.g. the hydrogen atom(s) in the CH₂ or NH moieties of X⁵, X⁶ and/or X⁷.

R⁵ can be bound to any of the ring members X⁵, X⁶ and/or X⁷, but if X⁷ is NH or CH₂, R⁵ is preferably bound to X⁷, where it replaces a hydrogen atom of this NH or CH₂ group X⁷ (so that X⁷ is NR⁵ or CHR⁵ or C(R⁴)R⁵).

If X³, X⁴, X⁵, X⁶ or X⁷ are NH, preferably they do not carry an N-bound radical R³, R⁴ or R⁵.

In a preferred embodiment, X¹ is NH or CH₂, and in particular NH.

In a preferred embodiment, X³, X⁴, X⁵ and X⁶, independently of each other, are selected from —CH₂— and —CH₂CH₂—.

In a preferred embodiment, X⁷ is NH or CH₂, and in particular NH.

In a particular embodiment, if X² is CH, X¹ is simultaneously NH or O, especially NH.

A is preferably phenyl or pyridyl, in particular phenyl or 3-pyridyl, where A carries one substituent R⁶ and optionally one substituent R⁷.

In a preferred embodiment, A is phenyl or 3-pyridyl, and carries the radical R⁶ in the 2-position and the radical R⁷, if present, in the 4- or 5-position, relative to the 1-position of the attachment point of A to the remainder of the molecule.

18

In particular, A is phenyl or 3-pyridyl, and carries the radical R⁶ in the 2-position, relative to the 1-position of the attachment point of A to the remainder of the molecule, and carries no radical R⁷.

B is preferably phenyl or 2-pyridyl, where B may carry 1, 2 or 3 substituents R⁸.

In case that B is 2-pyridyl and carries one substituent R⁸, this is preferably bound in the 4-position, relative to the 1-position of the attachment point of B to the remainder of the molecule (i.e. to the sulfonyl group).

In case that B is phenyl and carries one substituent R⁸, this is preferably bound in the 2- or 4-position, relative to the 1-position of the attachment point of B to the remainder of the molecule (i.e. to the sulfonyl group).

In case that B is 2-pyridyl and carries two substituents R⁸, these are preferably bound in the 4- and 5- or 4- and 6-positions, relative to the 1-position of the attachment point of B to the remainder of the molecule (i.e. to the sulfonyl group).

In case that B is phenyl and carries two substituents R⁸, these are preferably bound in the 2- and 4-positions, relative to the 1-position of the attachment point of B to the remainder of the molecule (i.e. to the sulfonyl group).

In case that B is phenyl and carries three substituents R⁸, these are preferably bound in the 2-, 4- and 6-positions, relative to the 1-position of the attachment point of B to the remainder of the molecule (i.e. to the sulfonyl group).

R¹ is preferably selected from halogen and cyano, and in particular from cyano, fluorine and chlorine. Specifically, R¹ is cyano.

R² is preferably selected from hydrogen and halogen, and in particular from hydrogen and fluorine.

R³ and R⁴, independently of each other and independently of each occurrence, are preferably selected from halogen and C₁-C₄-alkyl, and in particular from F, Cl and CH₃, with the proviso that R³ and R⁴ are not halogen if they are bound to a carbon atom in α -position to a nitrogen ring atom; and are in particular CH₃.

R⁵ is preferably selected from hydrogen, C₁-C₆-alkyl, fluorinated C₁-C₆-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₆-alkyl which carries one substituent R¹¹; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that R⁵ is bound to a carbon ring atom, it is additionally selected from —OR¹³; where R¹¹, R¹² and R¹³ have one of the above general or, in particular, one of the below preferred meanings.

More preferably, R⁵ is selected from hydrogen, C₁-C₆-alkyl, fluorinated C₁-C₆-alkyl, C₁-C₆-alkyl which carries one substituent R¹¹; a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members; and a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that R⁵ is bound to a carbon ring atom, it is additionally

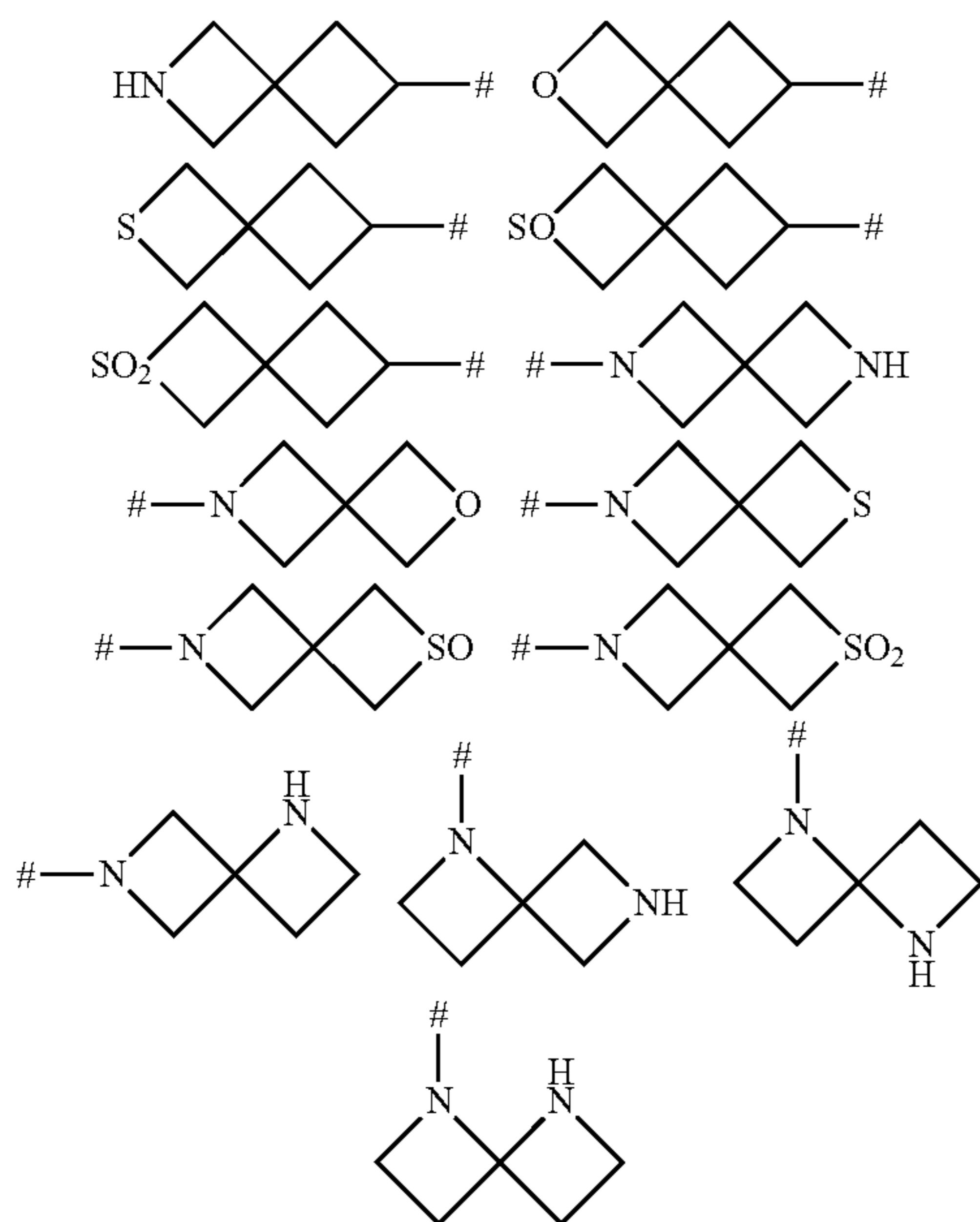
19

selected from $-\text{OR}^{13}$; where R^{11} , R^{12} and R^{13} have one of the above general or, in particular, one of the below preferred meanings.

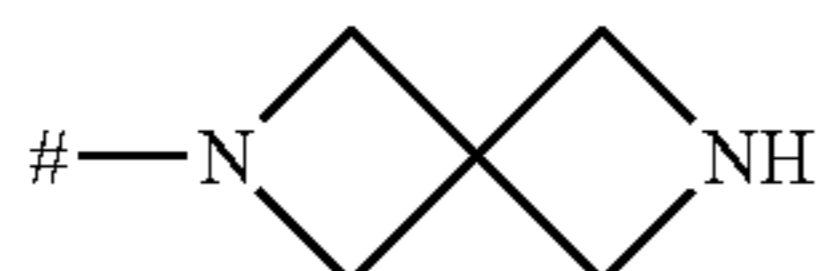
In particular, R^5 is selected from hydrogen, $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_4$ -alkyl which carries one substituent R^{11} ; a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from O, N and S as ring members; and a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic spiro ring containing 1 or 2 heteroatoms selected from O, N and S as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1 or 2 substituents R^{12} ; and in case that R^5 is bound to a carbon ring atom, it is additionally selected from $-\text{OR}^{13}$; where R^{11} , R^{12} and R^{13} have one of the above general or, in particular, one of the below preferred meanings.

The 4-, 5- or 6-membered saturated heteromonocyclic ring R^5 containing 1 or 2 heteroatoms selected from O, N and S as ring members is in particular selected from oxetan-3-yl, azetidin-3-yl, pyrrolidin-3-yl, piperidin-4-yl, piperazin-1-yl and morpholin-4-yl, and specifically from oxetan-3-yl, azetidin-3-yl, piperidin-4-yl, piperazin-1-yl and morpholin-4-yl.

The 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic spiro ring R^5 containing 1 or 2 heteroatoms selected from O, N and S as ring members is in particular selected from the following bicyclic radicals:



and is specifically



R^{11} is preferably selected from cyano, $-\text{OR}^{13}$; $\text{NR}^{14}\text{R}^{15}$; a 3-, 4-, 5-, 6- or 7-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members, and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members, where the heteromonocyclic or heterobicy-

20

clic ring may carry 1, 2 or 3 substituents R^{12} ; and as a substituent on a cycloalkyl ring, R^{11} is additionally selected from $\text{C}_1\text{-C}_4$ -alkyl and $\text{C}_1\text{-C}_4$ -haloalkyl; where R^{12} , R^{13} , R^{14} and R^{15} have one of the above general or, in particular, one of the below preferred meanings.

In particular, R^{11} is selected from $\text{NR}^{14}\text{R}^{15}$, where R^{14} and R^{15} are independently selected from hydrogen and $\text{C}_1\text{-C}_4$ -alkyl; and a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members, where the heteromonocyclic ring may carry 1 or 2 or 3 substituents R^{12} , where R^{12} has one of the above general or, in particular, one of the below preferred meanings.

The 4-, 5- or 6-membered saturated heteromonocyclic ring R^{11} containing 1 or 2 heteroatoms selected from O, N, S, NO, SO and SO_2 as ring members is in particular selected from oxetan-3-yl, azetidin-1-yl, azetidin-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, and morpholin-4-yl, and specifically from piperidin-1-yl, piperazin-1-yl and morpholin-4-yl.

R^{12} is preferably selected from halogen, cyano, $\text{C}_1\text{-C}_4$ -alkyl, fluorinated $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_4$ -alkoxy, fluorinated $\text{C}_1\text{-C}_4$ -alkoxy, phenyl which may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, $\text{C}_1\text{-C}_4$ -alkyl, fluorinated $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_4$ -alkoxy and fluorinated $\text{C}_1\text{-C}_4$ -alkoxy; and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members, where the heteromonocyclic ring may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, $\text{C}_1\text{-C}_4$ -alkyl, fluorinated $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_4$ -alkoxy and fluorinated $\text{C}_1\text{-C}_4$ -alkoxy, and in particular from $\text{C}_1\text{-C}_4$ -alkyl, fluorinated $\text{C}_1\text{-C}_4$ -alkyl, and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from O, N and S as ring members.

The 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring R^{12} is in particular selected from oxetan-3-yl, azetidin-3-yl, pyrrolidin-3-yl, piperidin-4-yl, piperazin-1-yl, and morpholin-4-yl, and is specifically from oxetan-3-yl.

R^{13} is preferably selected from hydrogen, $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_4$ -haloalkyl and $\text{C}_1\text{-C}_4$ -alkyl which carries one substituent R^{17} ; and is in particular $\text{C}_1\text{-C}_4$ -alkyl which carries one substituent R^{17} ; where R^{17} has one of the above general or, in particular, one of the below preferred meanings.

R^{17} is preferably selected from $\text{NR}^{14}\text{R}^{15}$; phenyl which may carry 1, 2 or 3 substituents R^{12} ; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members; where R^{14} and R^{15} have one of the above general or, in particular, one of the below preferred meanings. More preferably R^{17} is a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO_2 as ring members, and in particular a 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N and S, such as piperidin-1-yl, piperazin-1-yl or, especially, morpholin-4-yl.

R^6 is preferably $\text{C}_1\text{-C}_3$ -alkoxy, preferably methoxy, ethoxy or isopropoxy; and in particular methoxy or ethoxy.

R^7 is preferably halogen or $\text{C}_1\text{-C}_3$ -alkoxy, in particular fluorine or methoxy.

Preferably each R^8 is independently selected from halogen, cyano, $\text{C}_1\text{-C}_3$ -alkyl, fluorinated $\text{C}_1\text{-C}_3$ -alkyl, $\text{C}_1\text{-C}_3$ -alkoxy and fluorinated $\text{C}_1\text{-C}_3$ -alkoxy, more preferably from

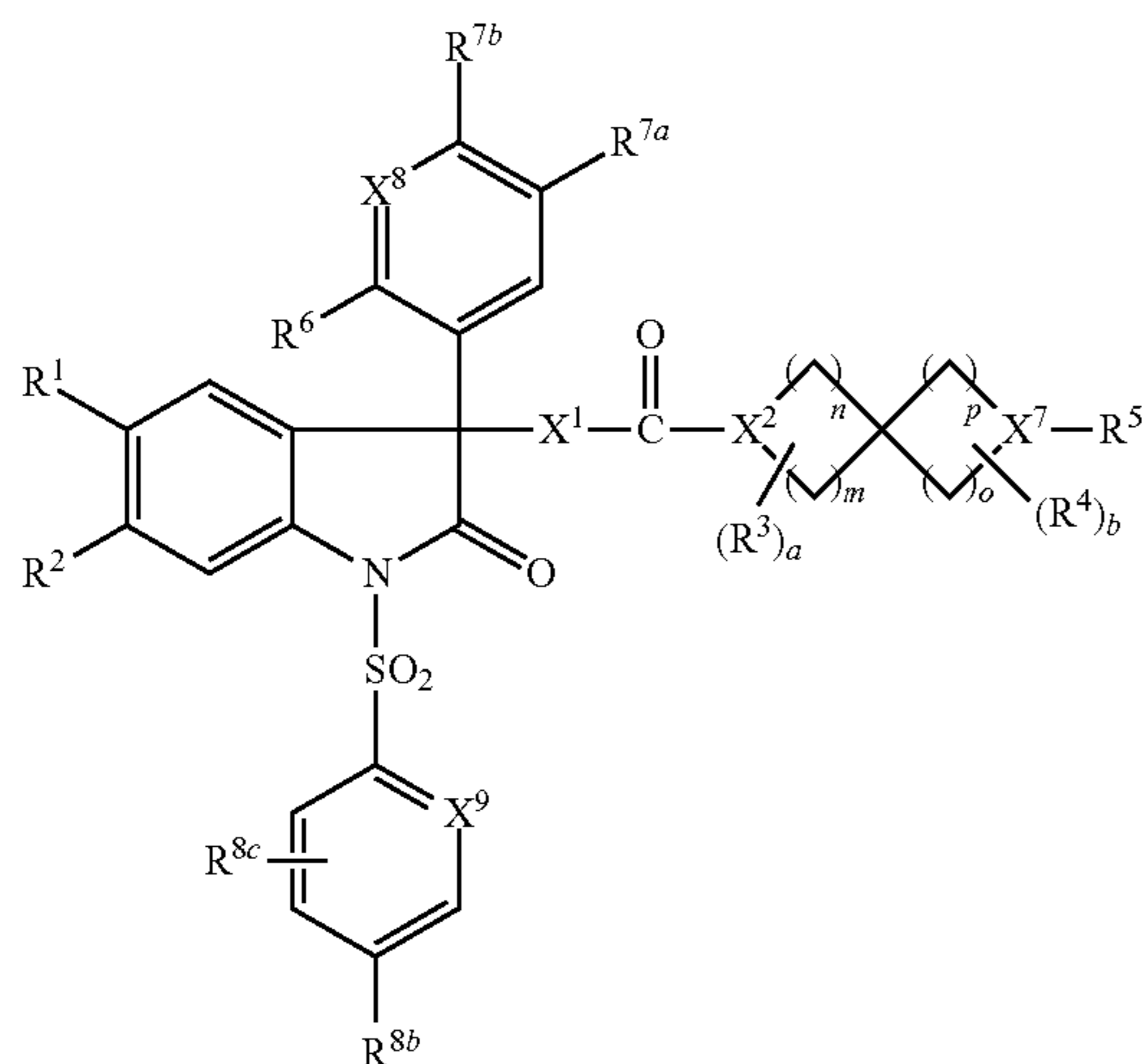
21

fluorine, cyano, methyl, methoxy and trifluoromethoxy, and in particular from fluorine, cyano, methyl and methoxy.

Preferably, a is 0 or 1, and in particular 0.

Preferably, b is 0 or 1, and in particular 0.

In a particular embodiment, the compound of formula I is a compound of formula IA



where

X^1 , X^2 , X^7 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , a and b have one of the above general or, in particular, one of the above preferred definitions (to be however more precise, X^7 is CH or N);

X^8 is N or CH;

X^9 is N or C— R^{8a} ;

R^{7a} and R^{7b} , independently of each other, are hydrogen or have one of the general or, in particular, one of the preferred definitions given above for R^7 ; and are in particular hydrogen;

R^{8a} , R^{8b} and R^{8c} , independently of each other, are hydrogen or have one of the general or, in particular, one of the preferred definitions given above for R^8 ; and

m, n, o and p are independently of each other 1 or 2.

Preferably, m and n are both 1 or are both 2.

Preferably, o and p are both 1 or are both 2.

The invention preferably relates to compounds of the formula 1A in which

X^1 is NH or CH_2 ;

X^2 is N or CH;

X^7 is N or CH;

X^8 is N or CH;

X^9 is N or CR^{8a};

R^1 is halogen or cyano;

R^2 is hydrogen or halogen;

R^3 and R^4 , independently of each other and independently of each occurrence, are selected from halogen and C₁-C₄-alkyl, with the proviso that R^3 and R^4 are not halogen if they are bound to a carbon atom in α -position to a nitrogen ring atom; and are in particular CH₃;

R^5 is selected from hydrogen, C₁-C₆-alkyl, fluorinated C₁-C₆-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₆-alkyl which carries one substituent R¹¹; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially

22

unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that X^7 is CH, R^5 is additionally selected from —OR¹³;

R^6 is C₁-C₃-alkoxy;

R^{7a} and R^{7b} , independently of each other, are hydrogen, halogen or C₁-C₃-alkoxy;

R^{8a} (if present), R^{8b} and R^{8c} , independently of each other, are selected from hydrogen, halogen, cyano, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R^{11} is selected from cyano, —OR¹³; NR¹⁴R¹⁵; a 3-, 4-, 5-, 6- or 7-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and as a substituent on a cycloalkyl ring, R^{11} is additionally selected from C₁-C₄-alkyl and C₁-C₄-haloalkyl;

R^{12} is selected from halogen, cyano, C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, C₁-C₄-alkoxy, fluorinated C₁-C₄-alkoxy, phenyl which may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, C₁-C₄-alkoxy and fluorinated C₁-C₄-alkoxy; and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1, 2 or 3 substituents selected from halogen, hydroxyl, cyano, C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, C₁-C₄-alkoxy and fluorinated C₁-C₄-alkoxy;

R^{13} is selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and C₁-C₄-alkyl which carries one substituent R¹⁷;

R^{14} and R^{15} , independently of each other, are selected from hydrogen and C₁-C₄-alkyl;

R^{17} is selected from NR¹⁴R¹⁵; phenyl which may carry 1, 2 or 3 substituents R¹²; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members;

a is 0 or 1;

b is 0 or 1;

m and n are both 1 or are both 2; and

o and p are both 1 or are both 2.

The invention more preferably relates to compounds of the formula IA in which

X^1 is NH or CH_2 ;

X^2 is N or CH;

X^7 is N or CH;

X^8 is N or CH;

X^9 is N or CR^{8a};

R^1 is cyano, fluorine or chlorine;

R^2 is hydrogen or fluorine;

R^5 is selected from hydrogen, C₁-C₆-alkyl, fluorinated C₁-C₆-alkyl, C₁-C₆-alkyl which carries one substituent R¹¹; a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members; and a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and

23

SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that X⁷ is CH, R⁵ is additionally selected from —OR¹³;

R⁶ is methoxy, ethoxy or isopropoxy;

R^{7a} and R^{7b}, independently of each other, are hydrogen, fluorine or methoxy;

R^{8a} (if present), R^{8b} and R^{8c}, independently of each other, are selected from hydrogen, fluorine, cyano, methyl, methoxy and trifluoromethoxy;

R¹¹ is selected from NR¹⁴R¹⁵ and a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1 or 2 or 3 substituents R¹²;

R¹² is selected from C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from O, N and S as ring members;

R¹³ is selected C₁-C₄-alkyl which carries one substituent R¹⁷;

R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁-C₄-alkyl;

R¹⁷ is a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members;

a is 0;

b is 0;

m and n are both 1 or are both 2; and

o and p are both 1 or are both 2.

In particular, the invention relates to compounds of the formula IA in which

X¹ is NH or CH₂;

X² is N or CH;

X⁷ is N or CH;

X⁸ is N or CH;

X⁹ is N or CR^{8a};

R¹ is cyano;

R² is hydrogen or fluorine;

R⁵ is selected from hydrogen, C₁-C₄-alkyl, C₁-C₄-alkyl which carries one substituent R¹¹; a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from O, N and S as ring members; and

a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic spiro ring containing 1 or 2 heteroatoms selected from O, N and S as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1 or 2 substituents R¹²; and in case that X⁷ is CH, R⁵ is additionally selected from —OR¹³;

R⁶ is methoxy or ethoxy;

R^{7a} and R^{7b} are hydrogen;

R^{8a} (if present) and R^{8b}, independently of each other, are selected from hydrogen, fluorine, cyano, methyl and methoxy;

R^{8c} is hydrogen;

R¹¹ is selected from NR¹⁴R¹⁵ and a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1 or 2 or 3 substituents R¹²;

R¹² is selected from C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from O, N and S as ring members;

24

R¹³ is selected C₁-C₄-alkyl which carries one substituent R¹⁷;

R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁-C₄-alkyl;

R¹⁷ is a 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from O, N and S;

a is 0;

b is 0;

m and n are both 1 or are both 2; and

o and p are both 1 or are both 2.

Examples of preferred embodiments of the present invention are compounds of the formulae I.1 to I.128 and the N-oxides, stereoisomers (inclusively the conformers) and the pharmaceutically acceptable salts thereof, in which the radicals X¹, R¹, R², R⁵, R^{8a}, R^{8b} and R^{8c} have one of the above general or preferred meanings. In particular, preferred compounds are the individual compounds compiled in the tables 1 to 53760 below.

Moreover, the meanings mentioned below for the individual variables in the tables are per se, independently of the combination in which they are mentioned, a particularly preferred embodiment of the substituents in question.

30

35

40

45

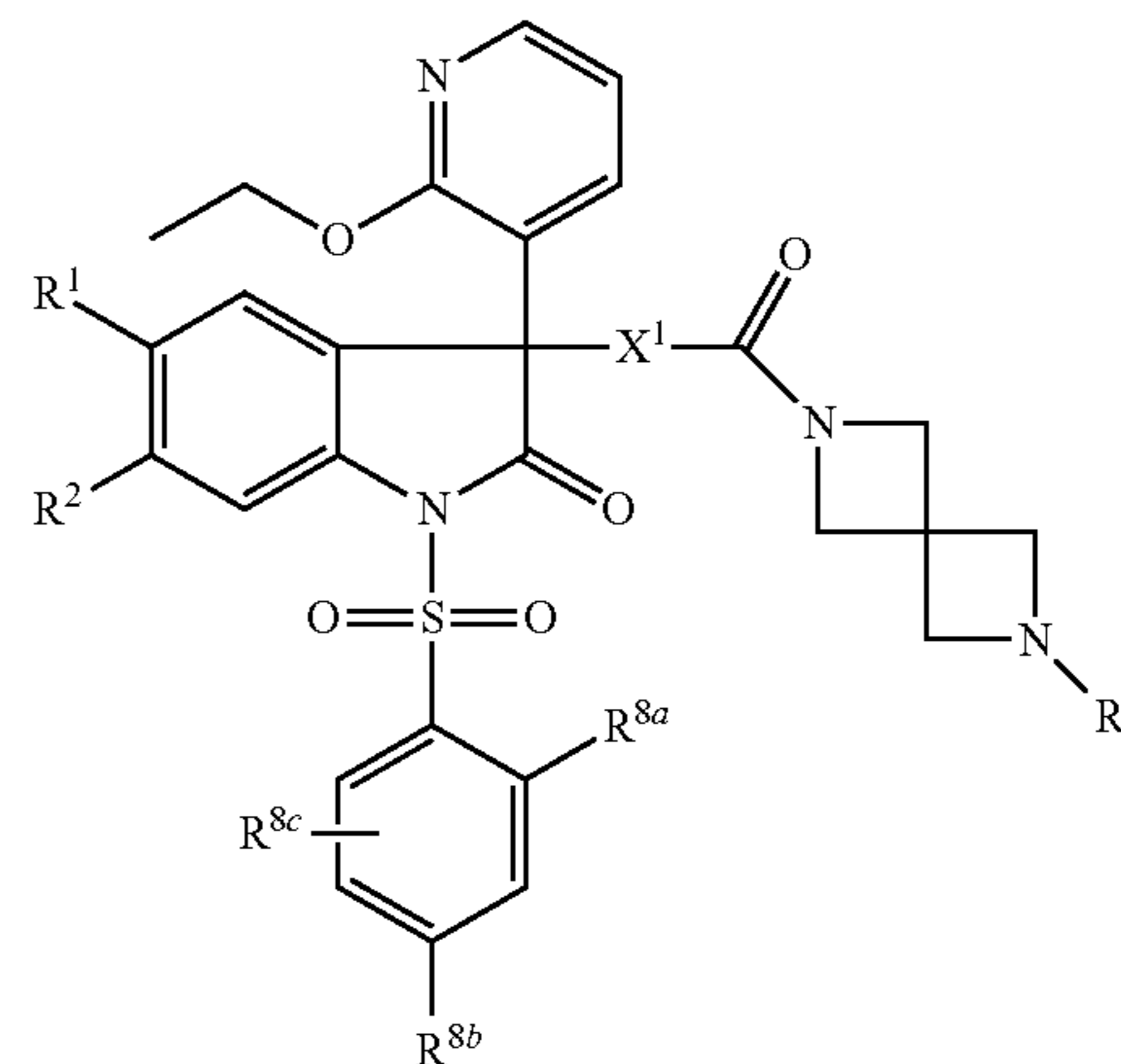
50

55

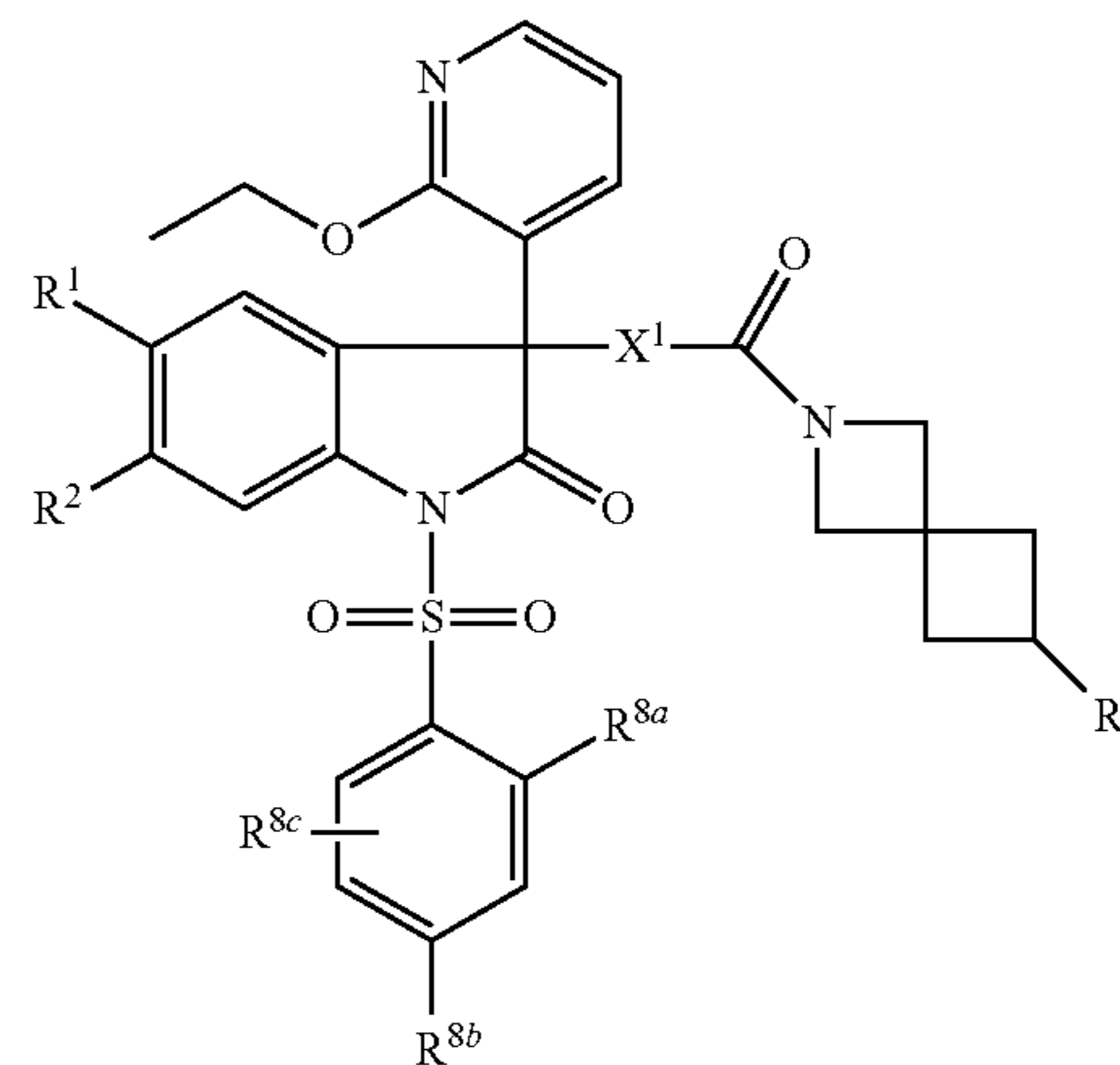
60

65

I.1

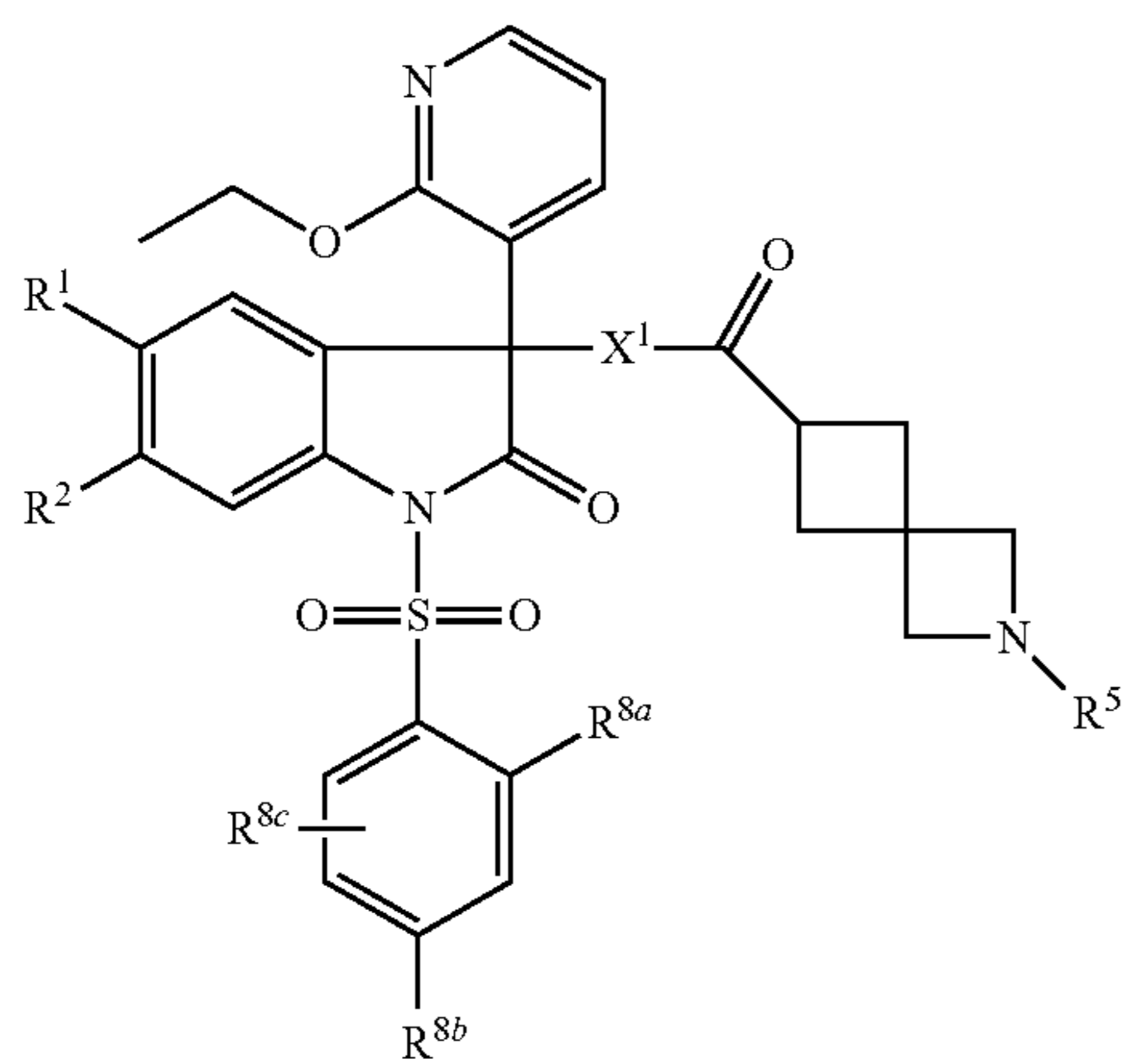


I.2



25

-continued



I.3

5

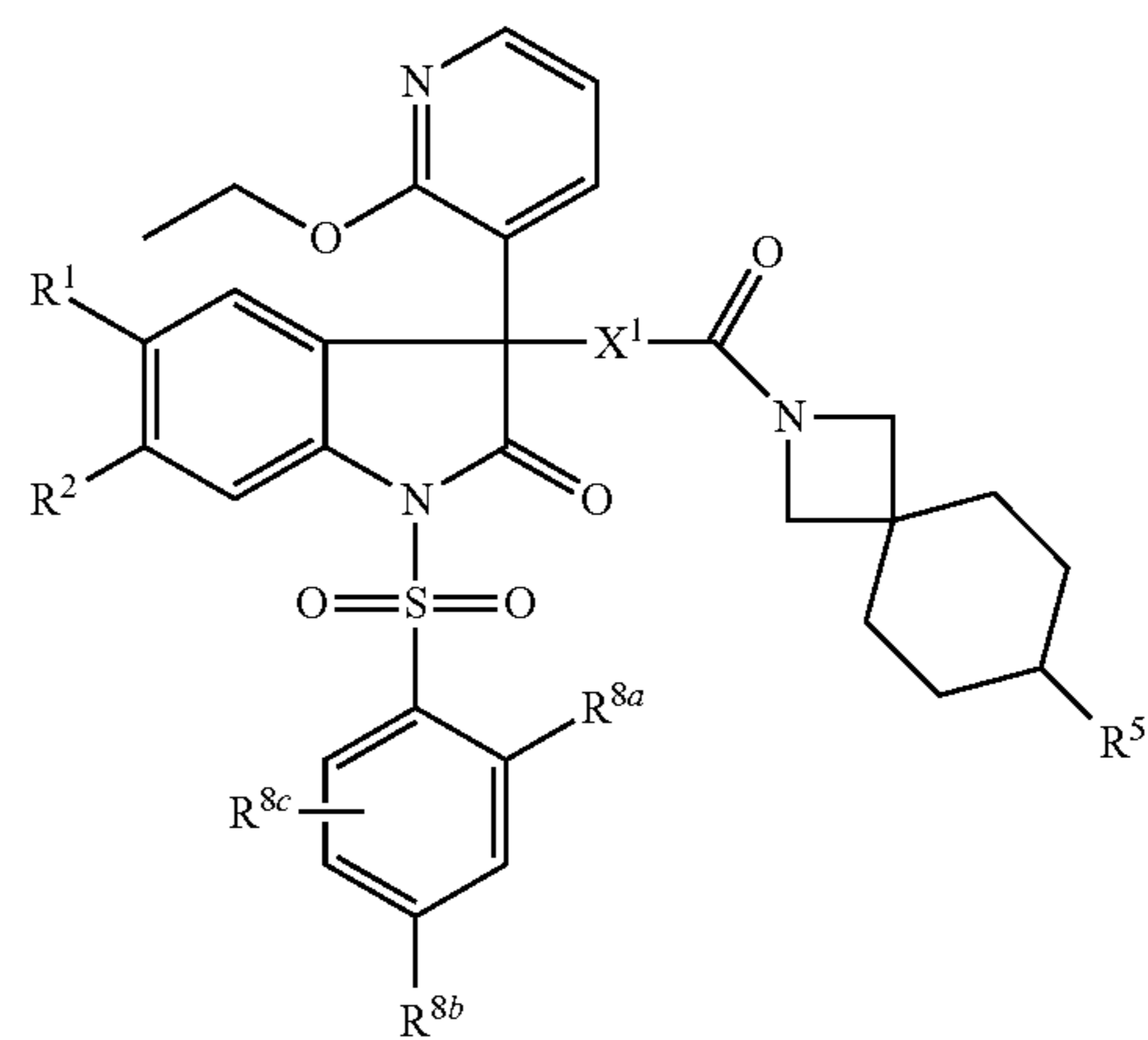
10

15

20

26

-continued



I.6

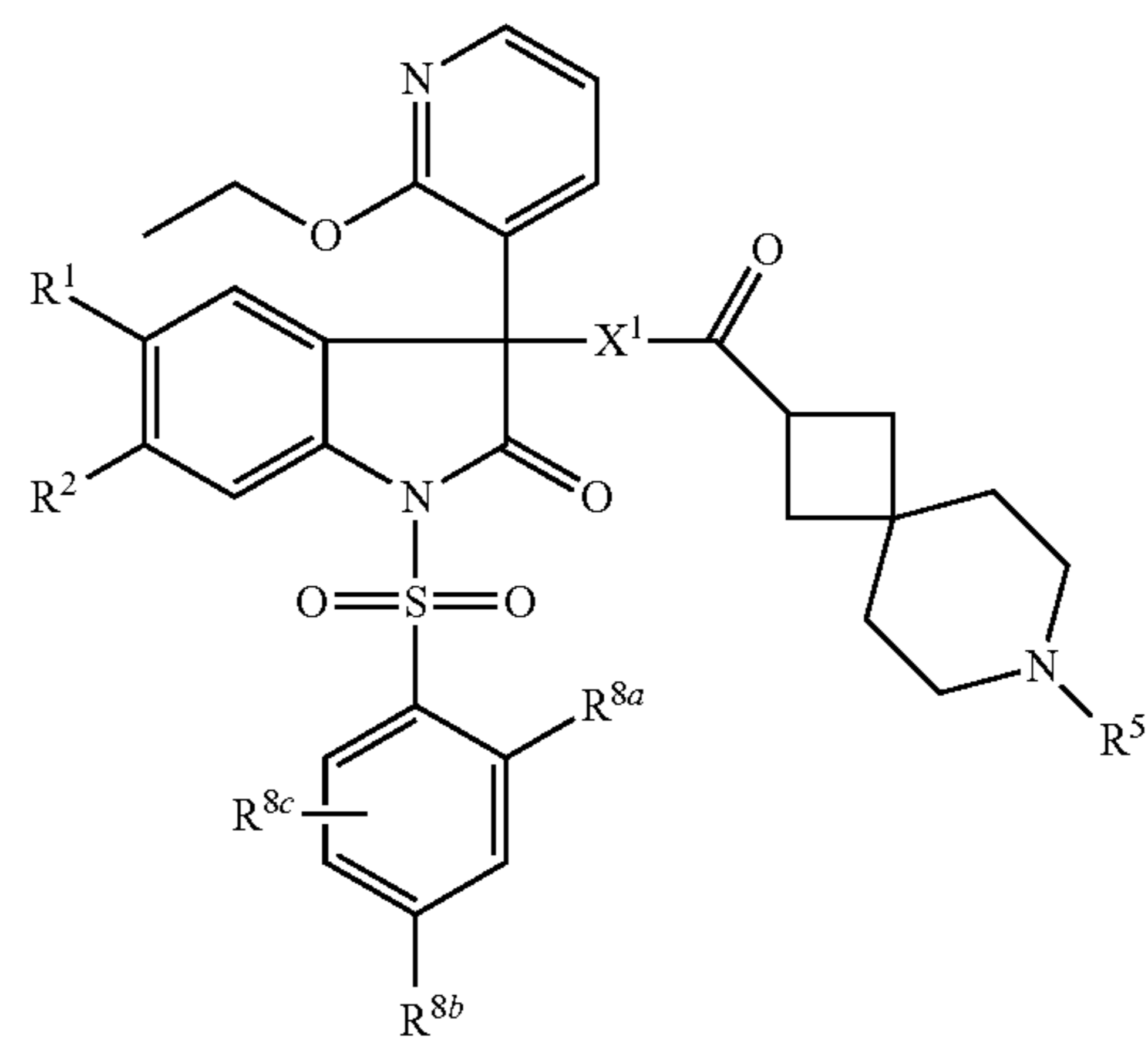
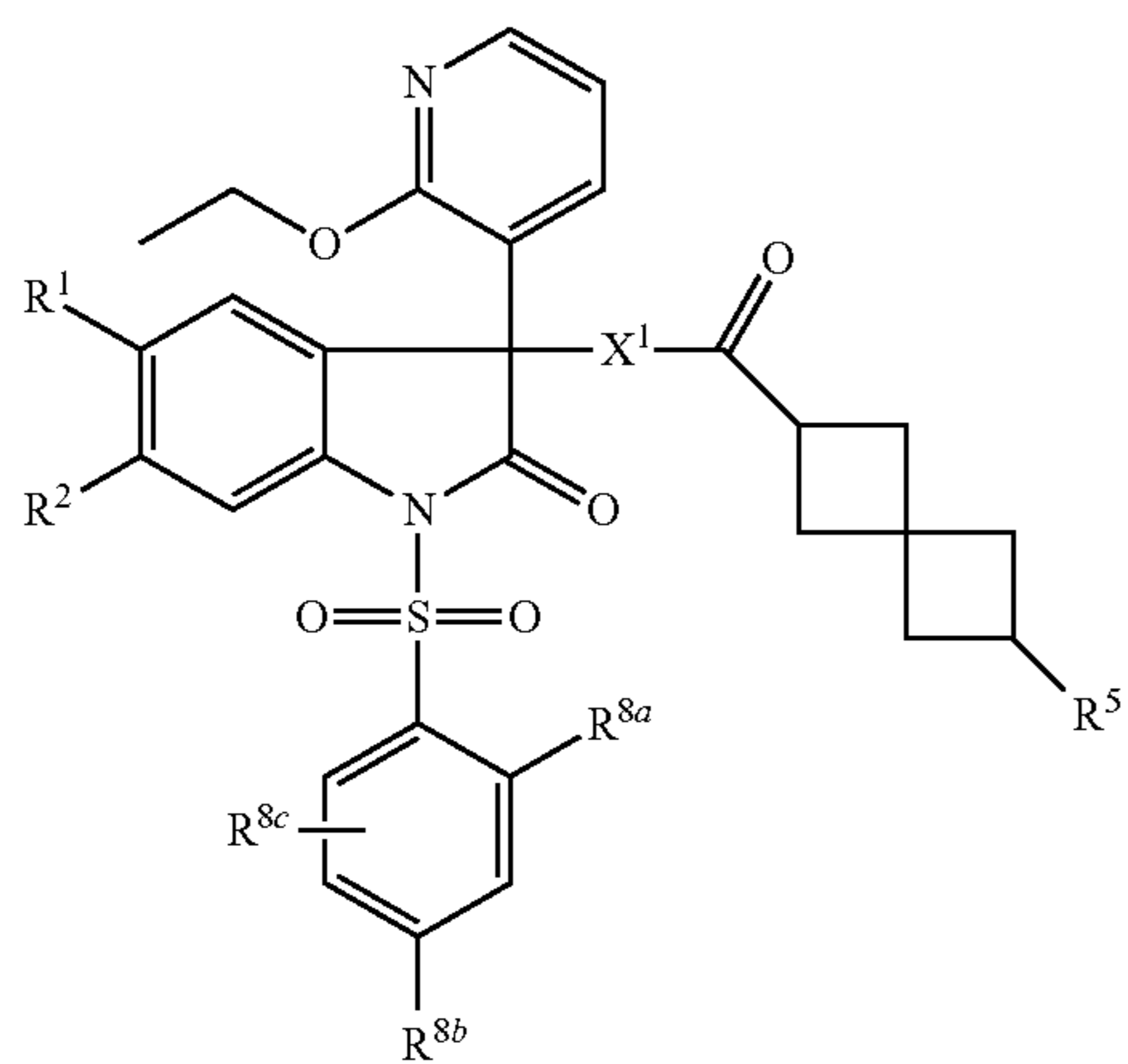
I.4

30

35

40

45



I.7

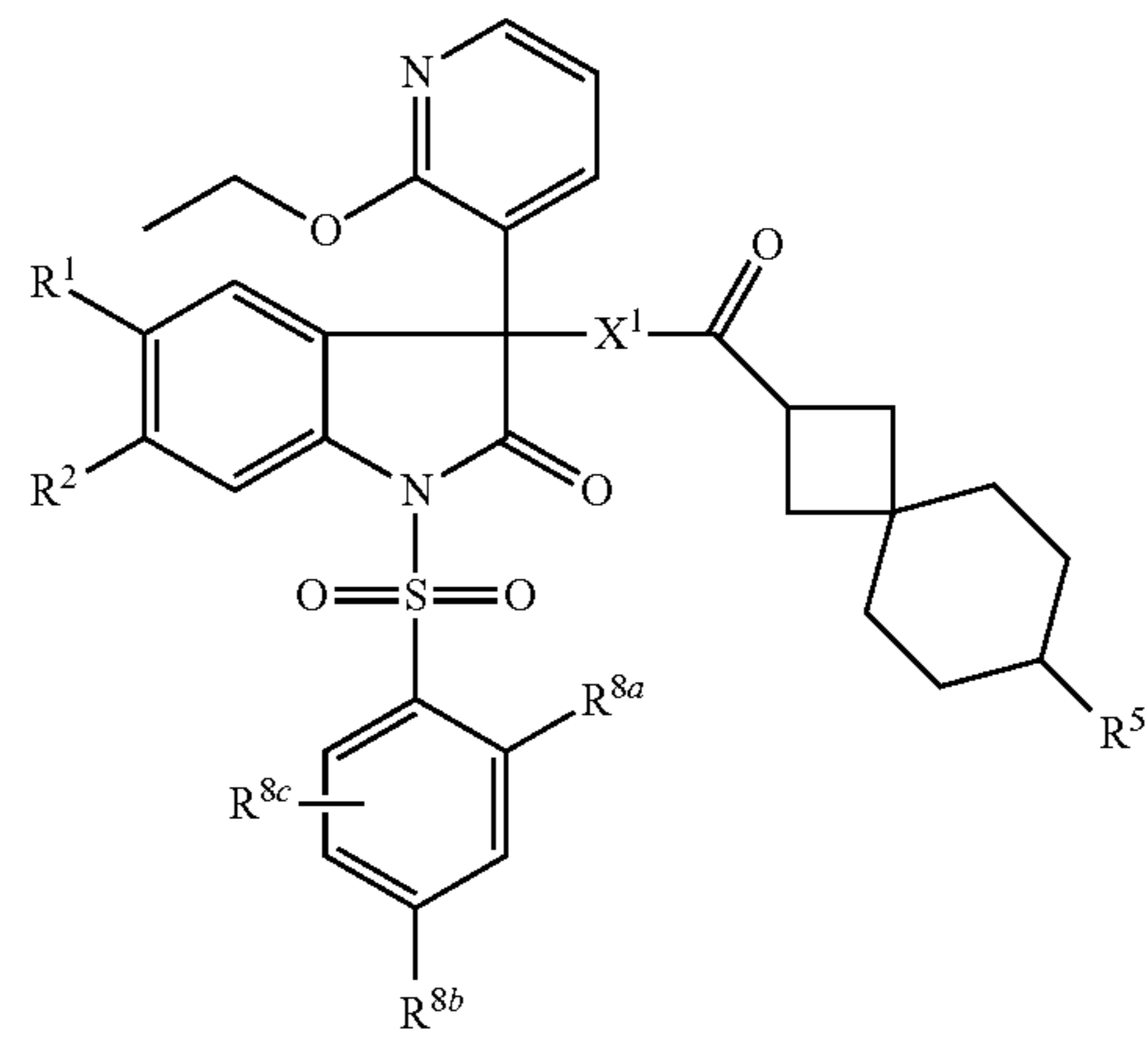
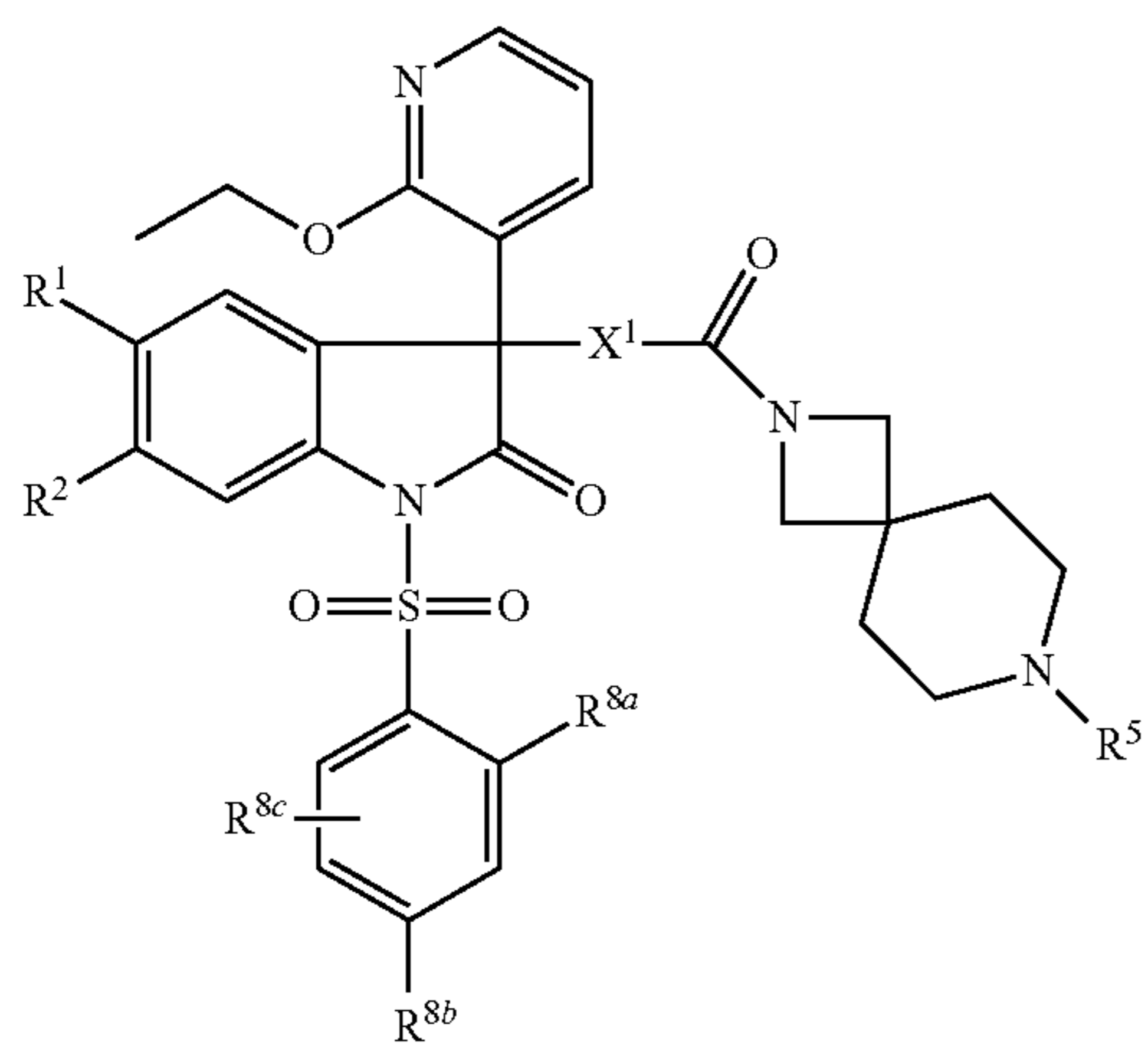
I.5

50

55

60

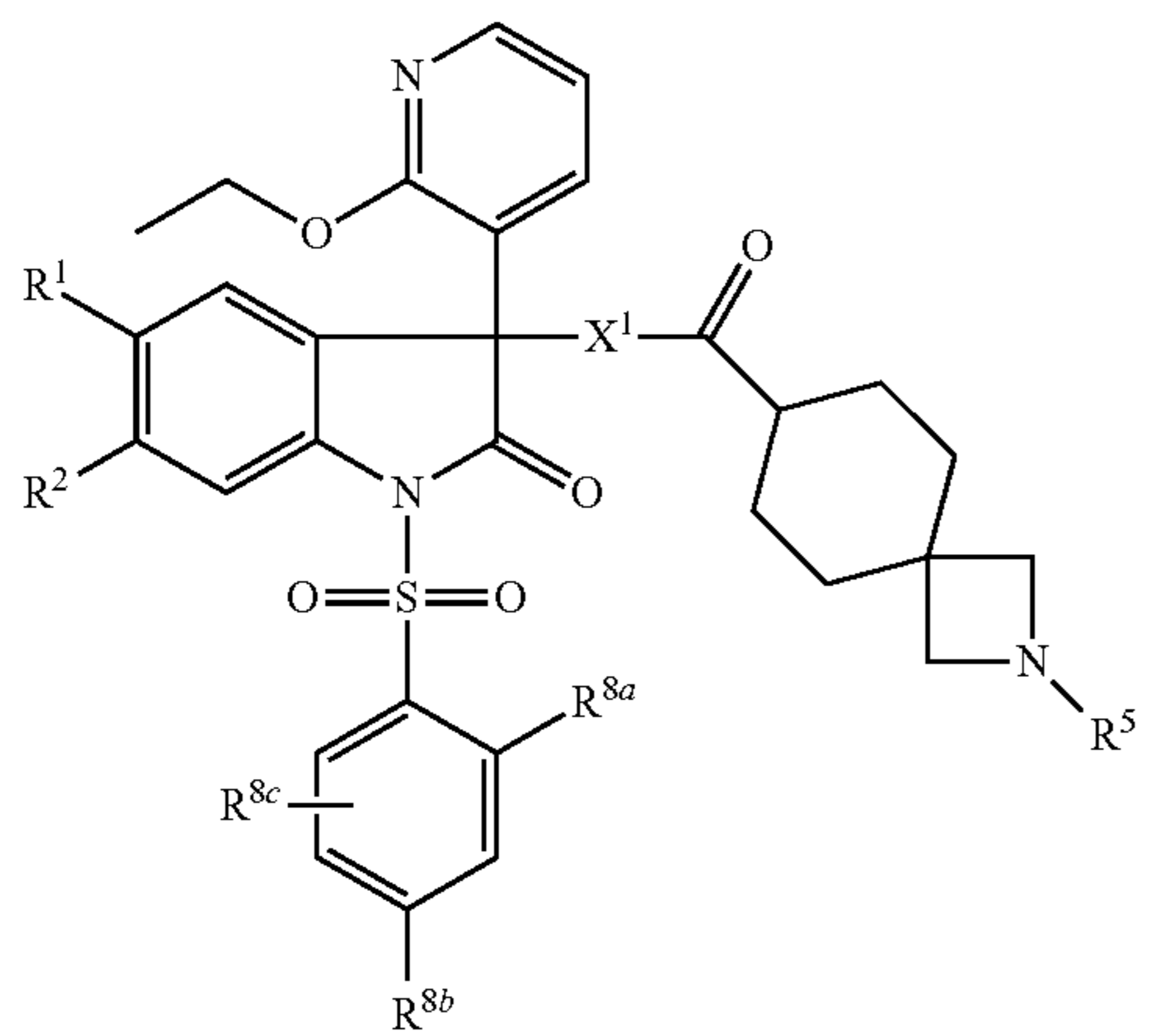
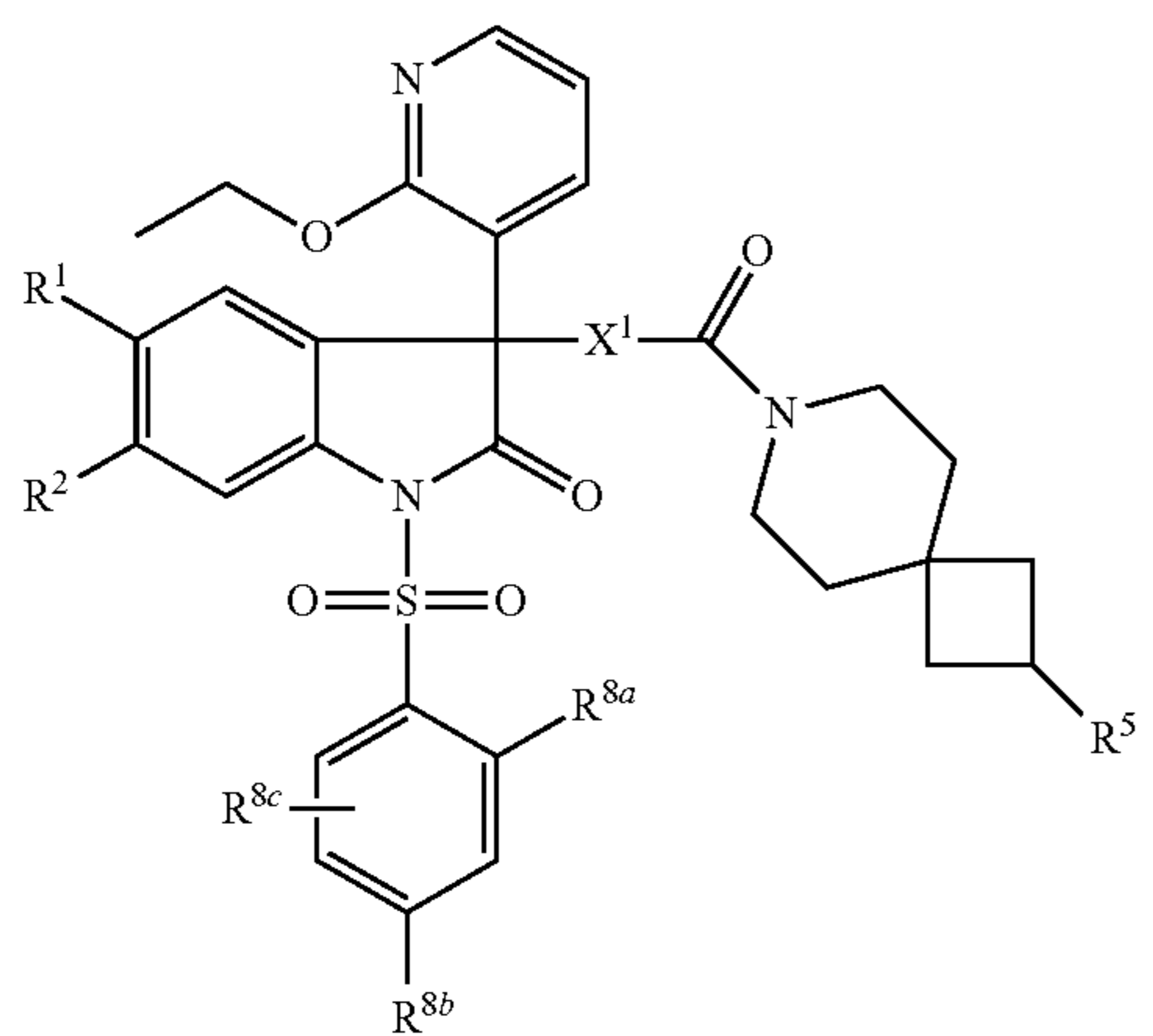
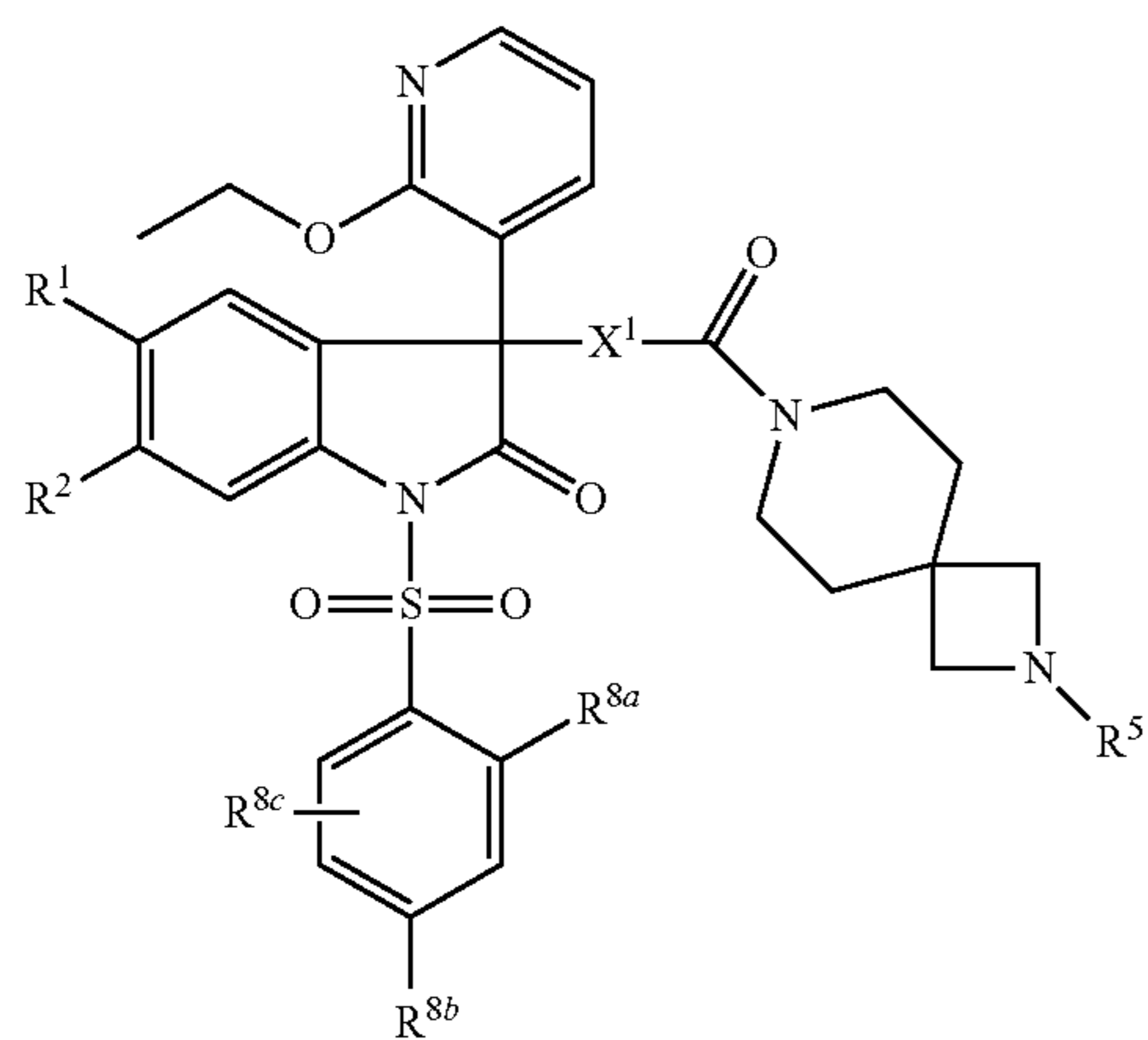
65



I.8

27

-continued



28

-continued

I.9

5

10

15

20

25

I.10

30

35

40

45

I.11

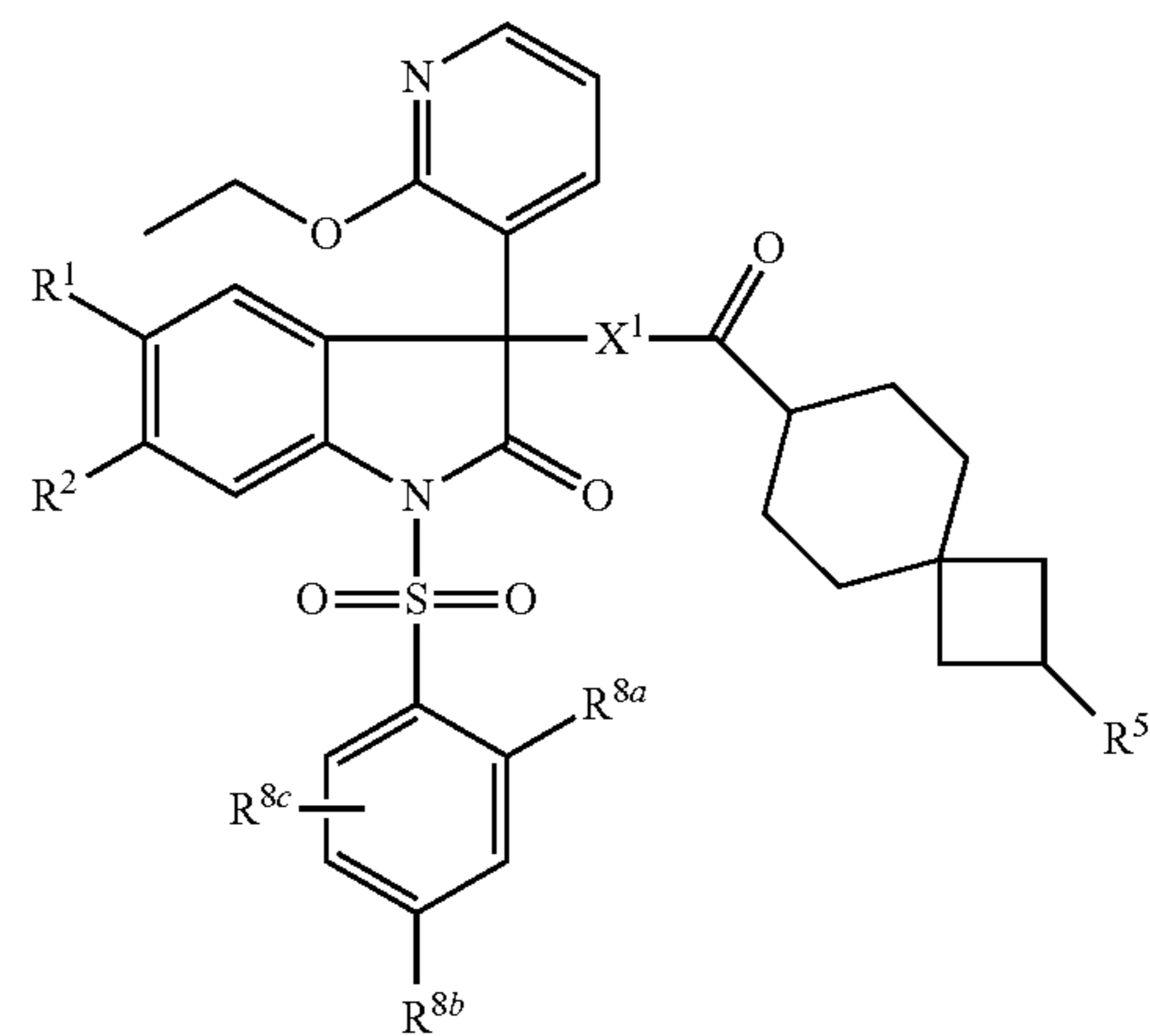
50

55

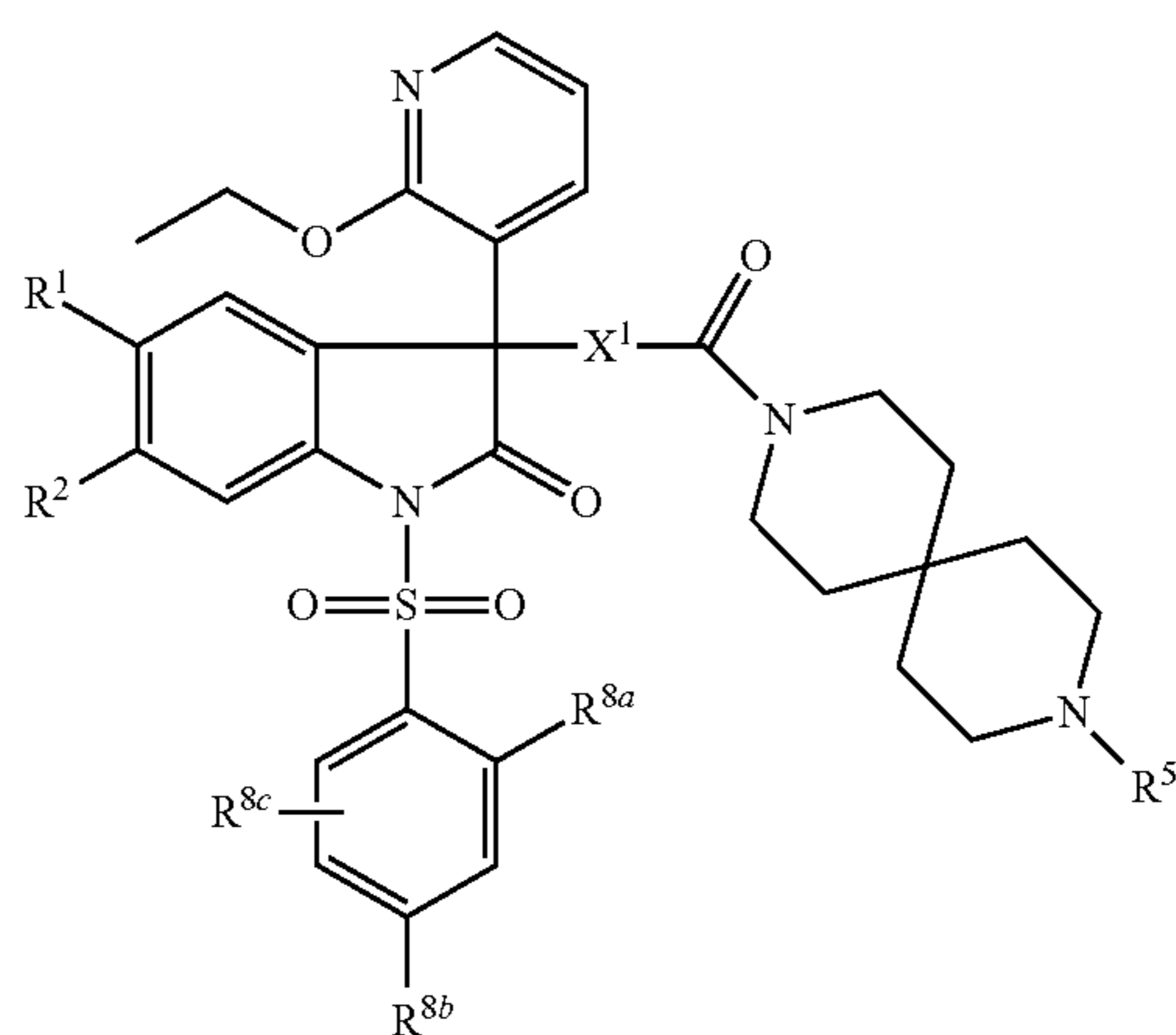
60

65

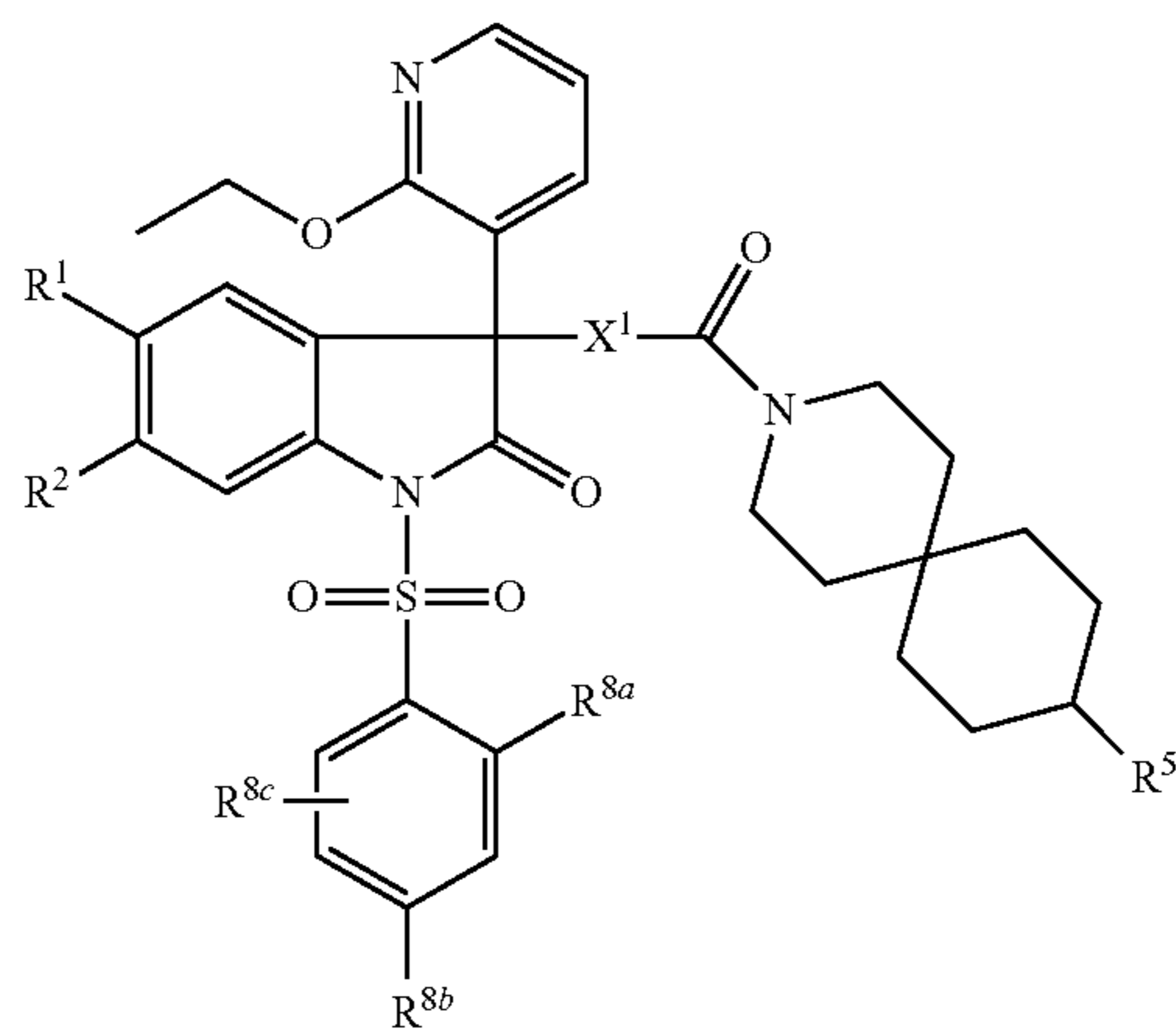
I.12



I.13

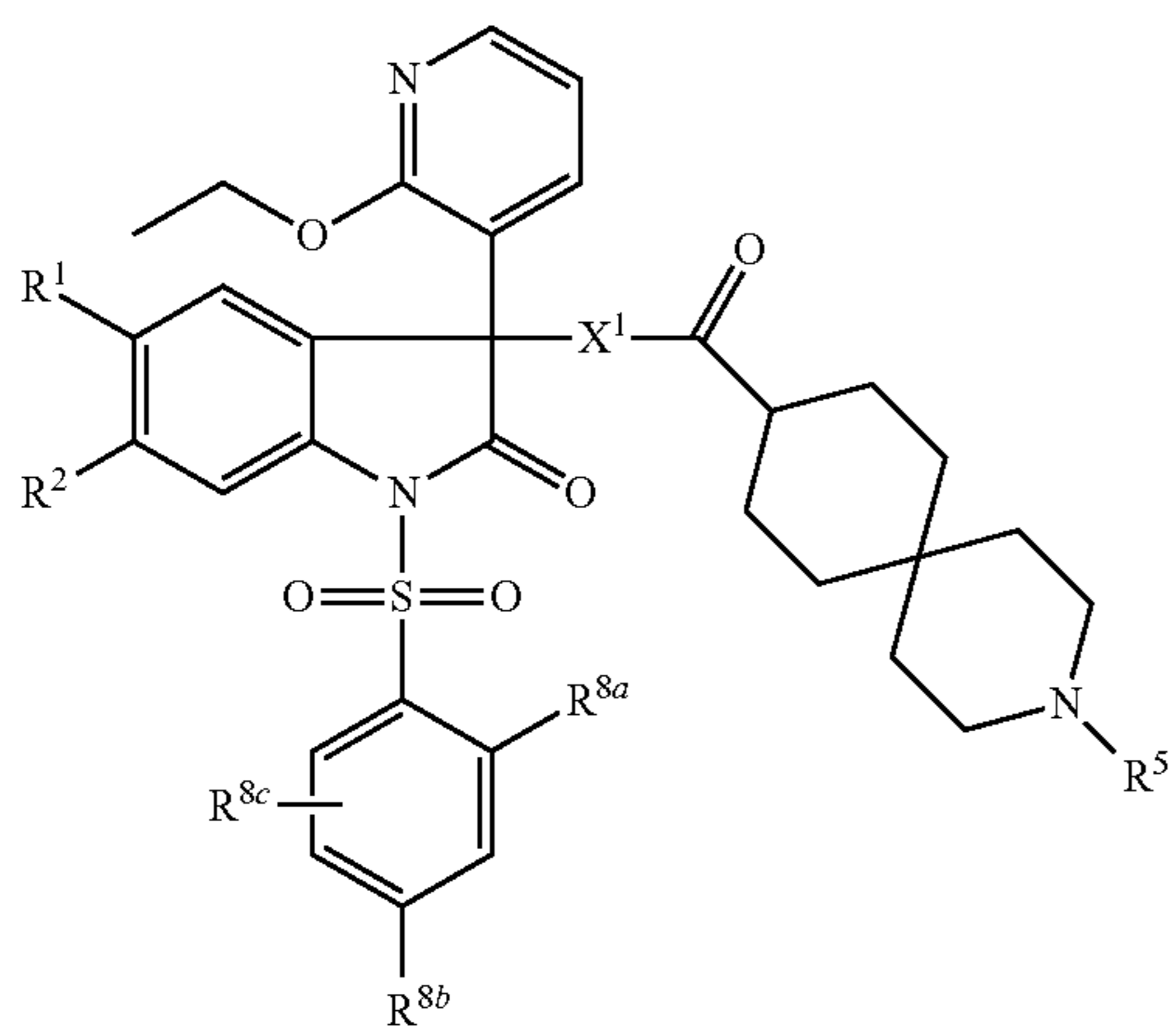


I.14



29

-continued



I.15

5

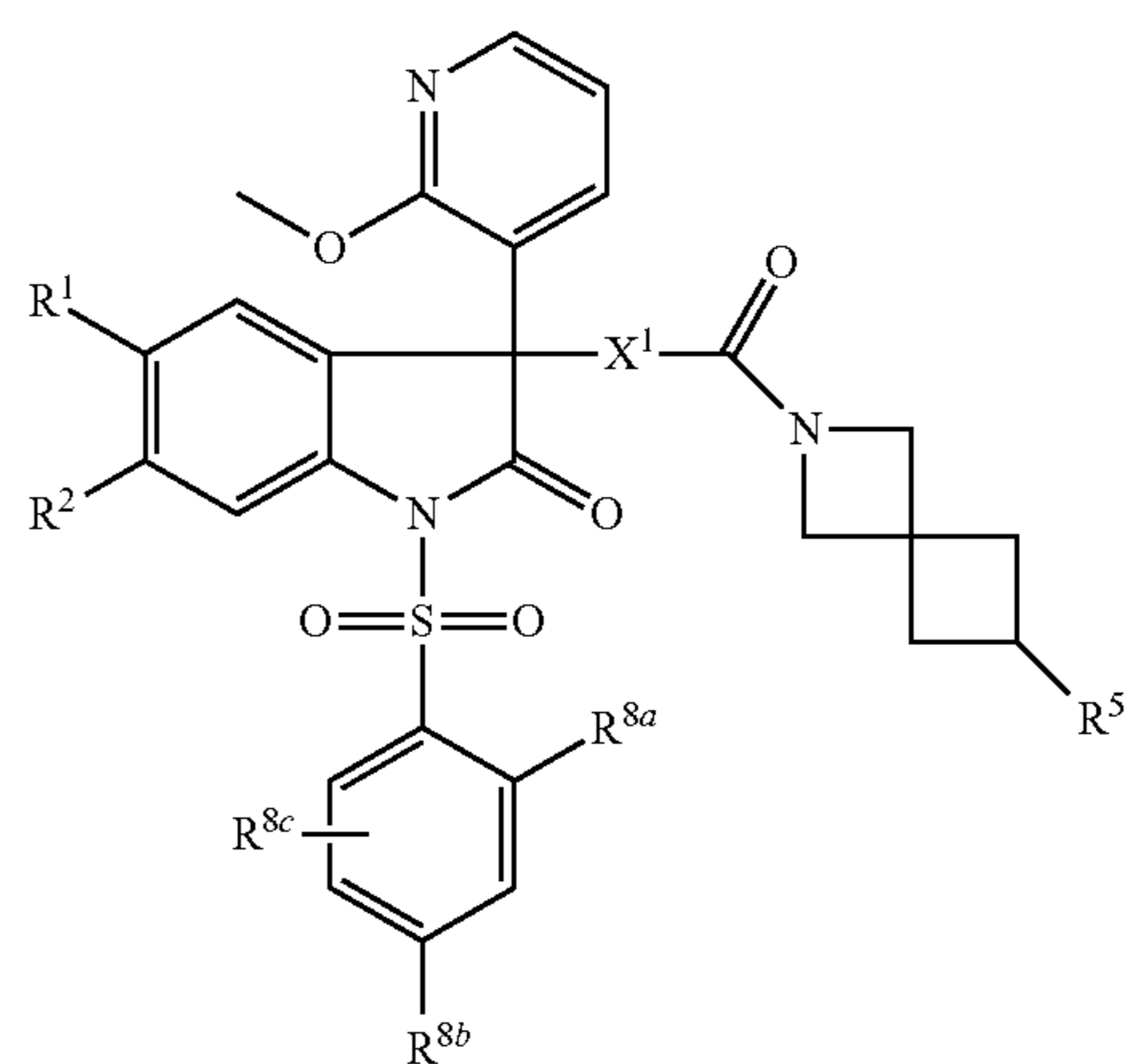
10

15

20

30

-continued



I.18

I.16

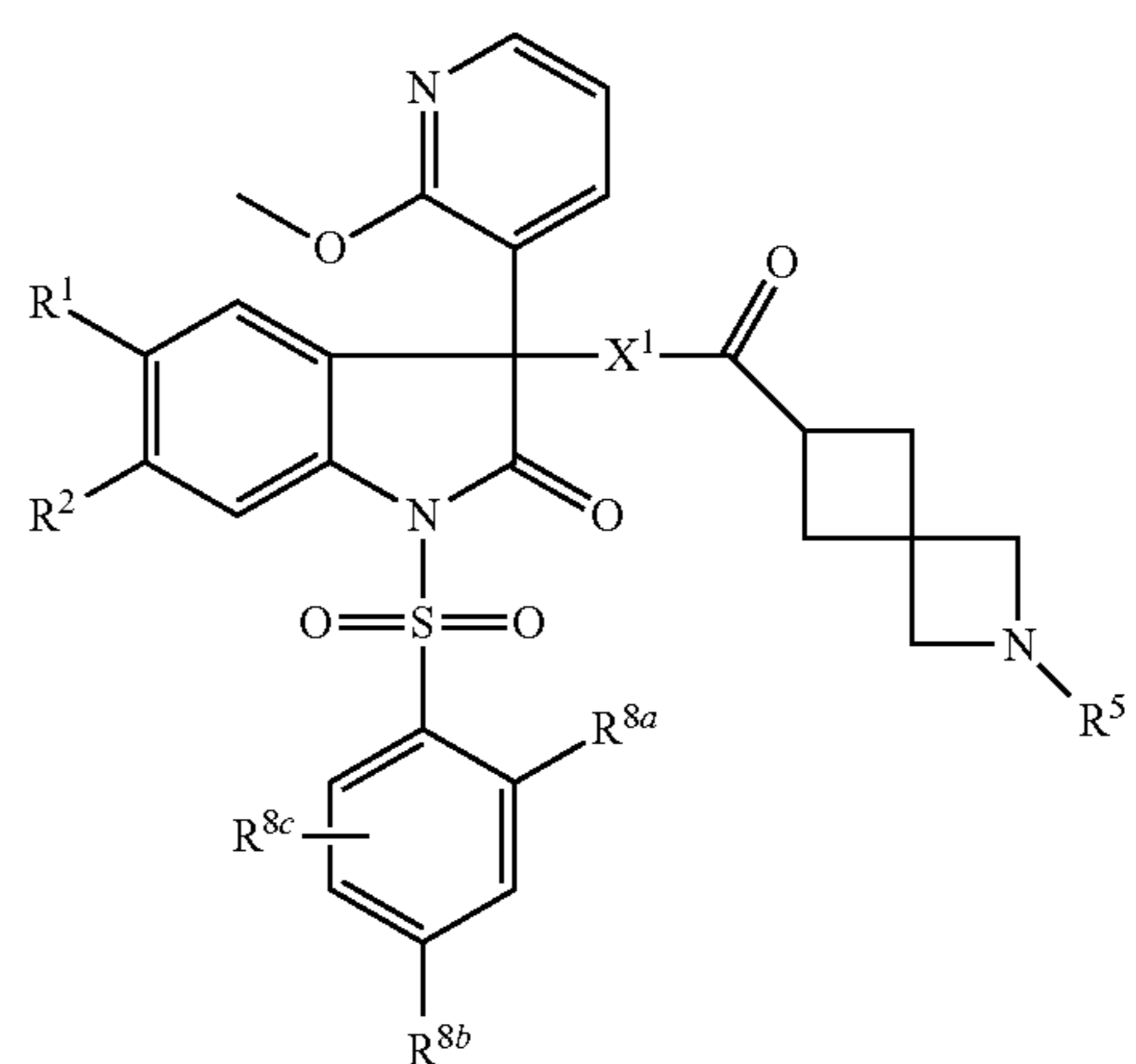
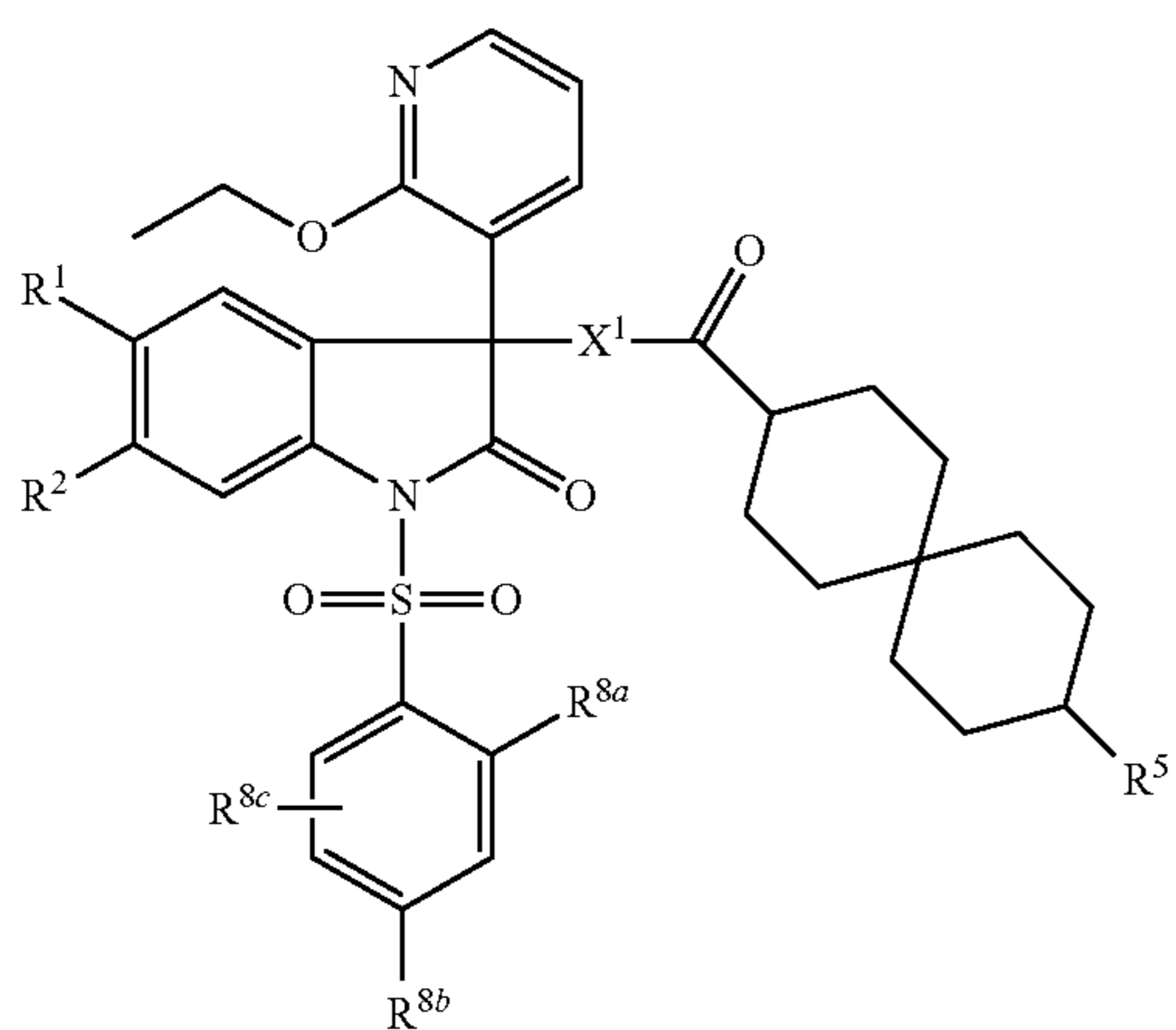
25

30

35

40

45



I.19

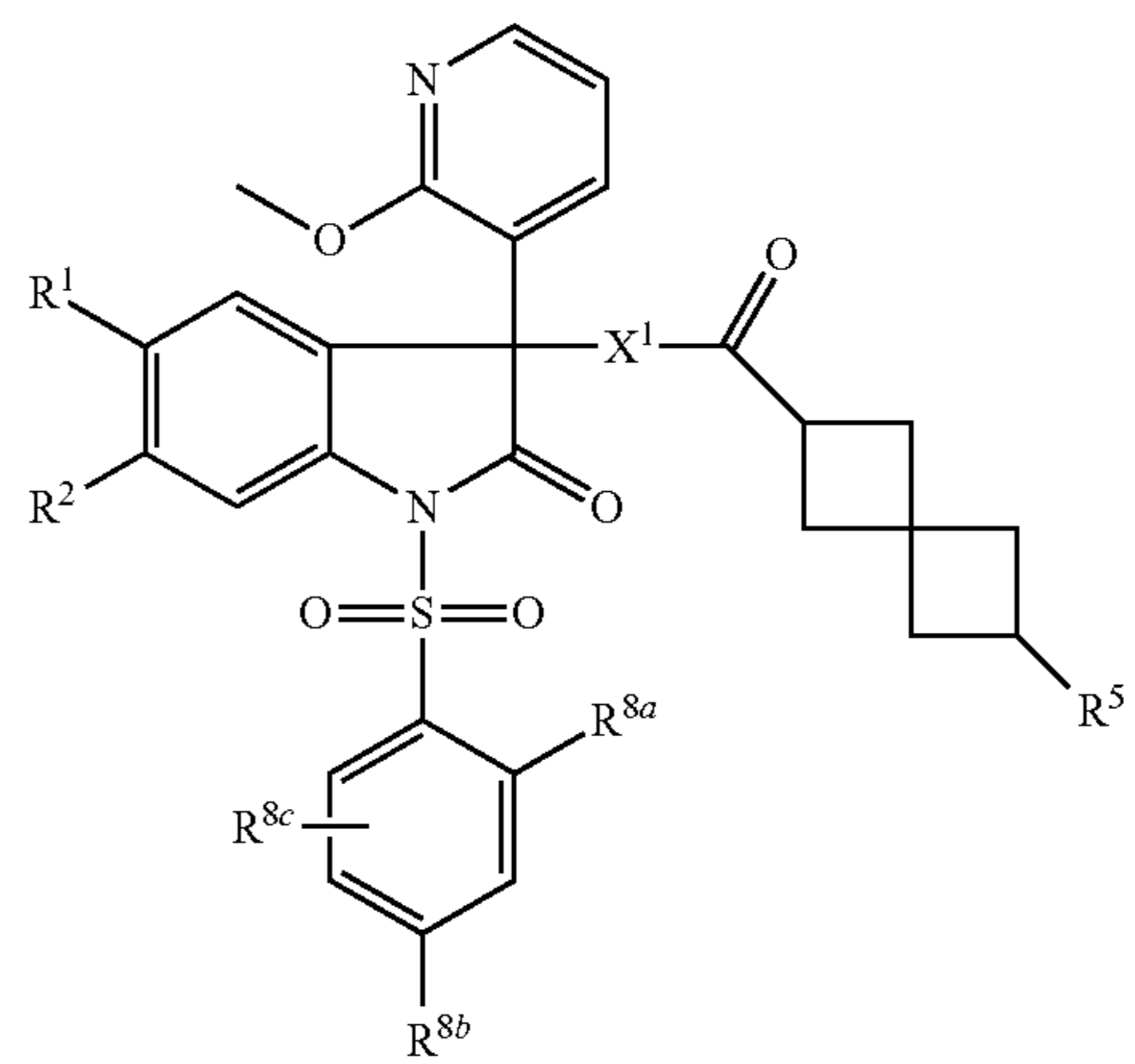
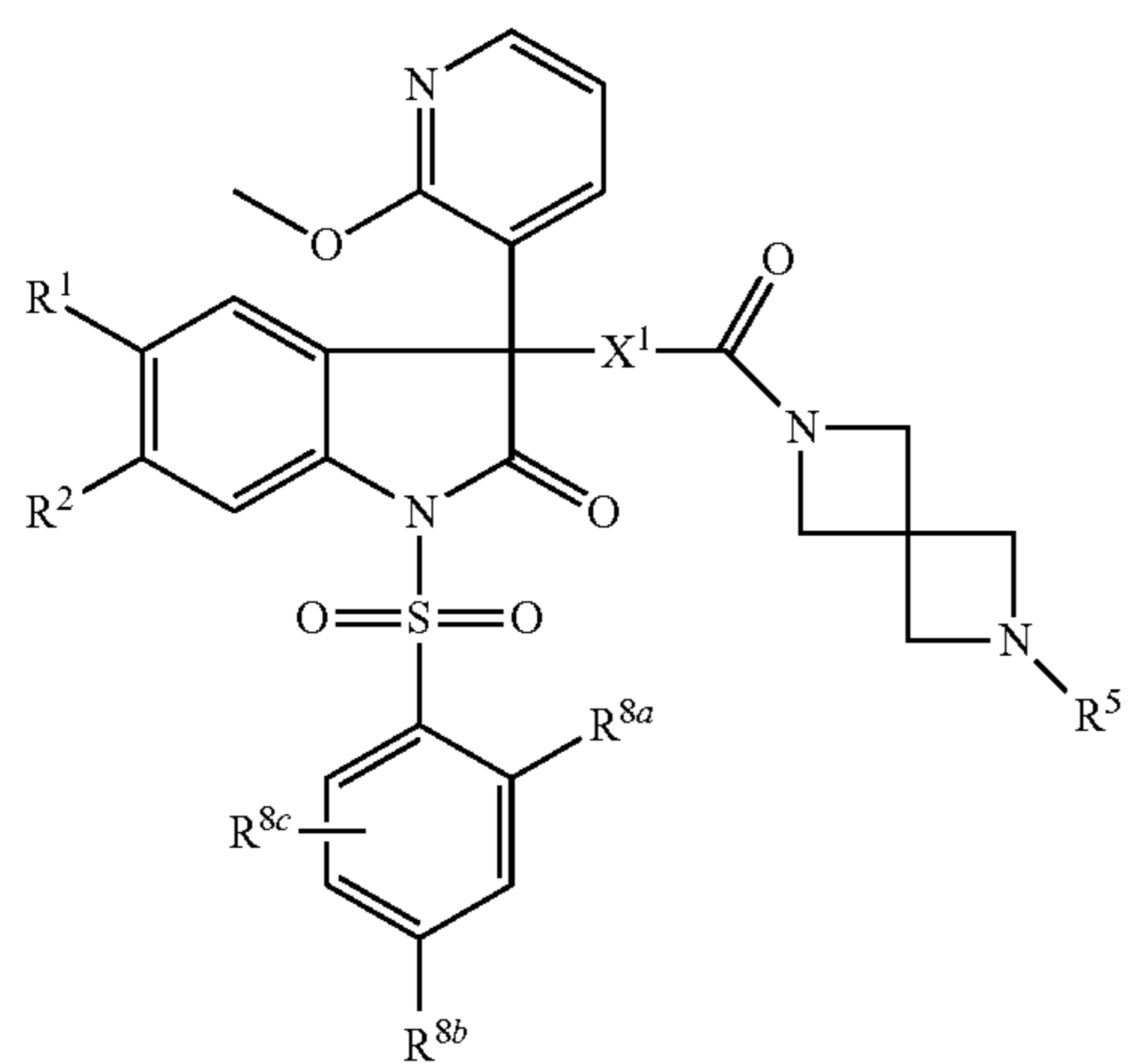
I.17

50

55

60

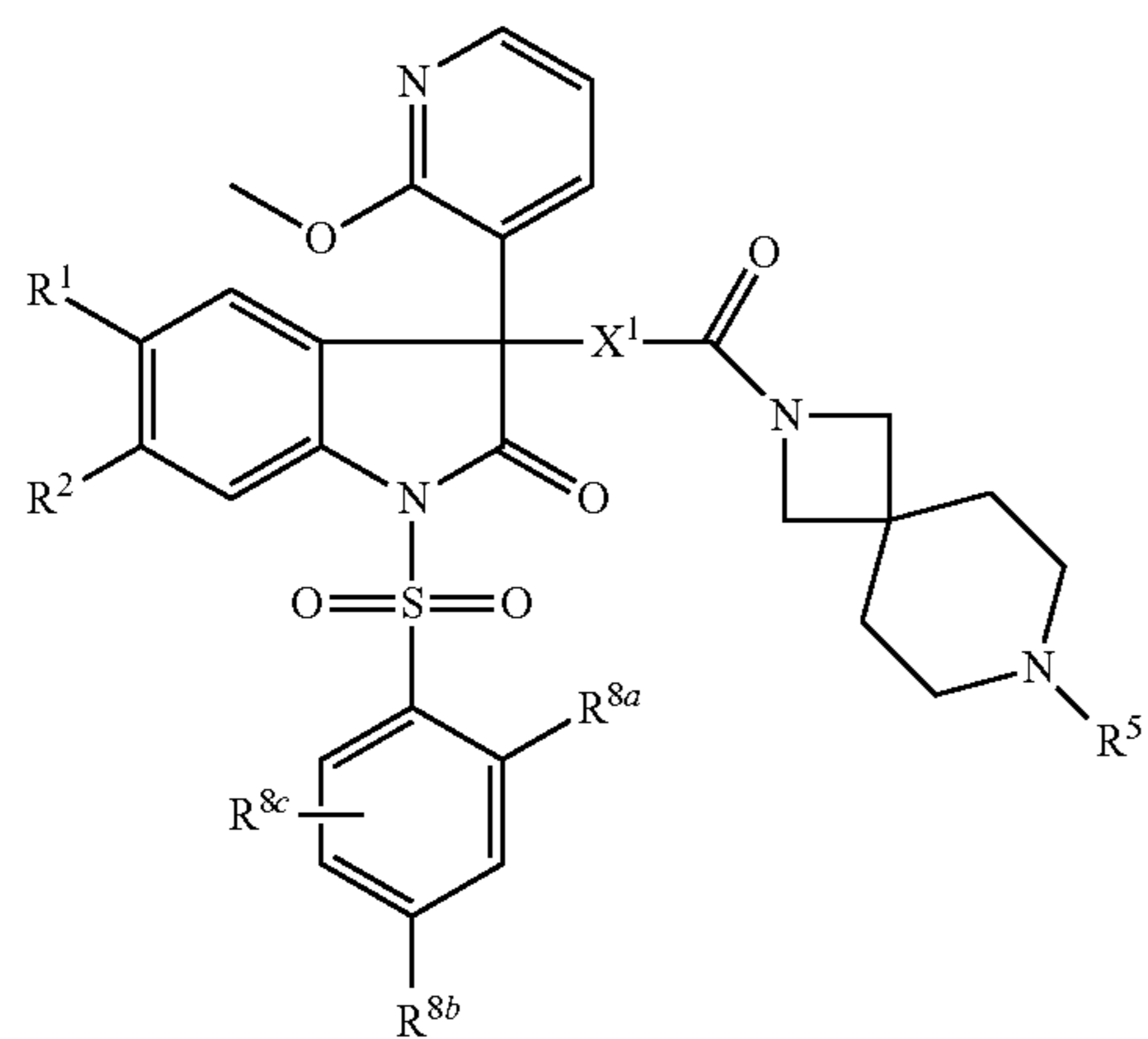
65



I.20

31

-continued



I.21

5

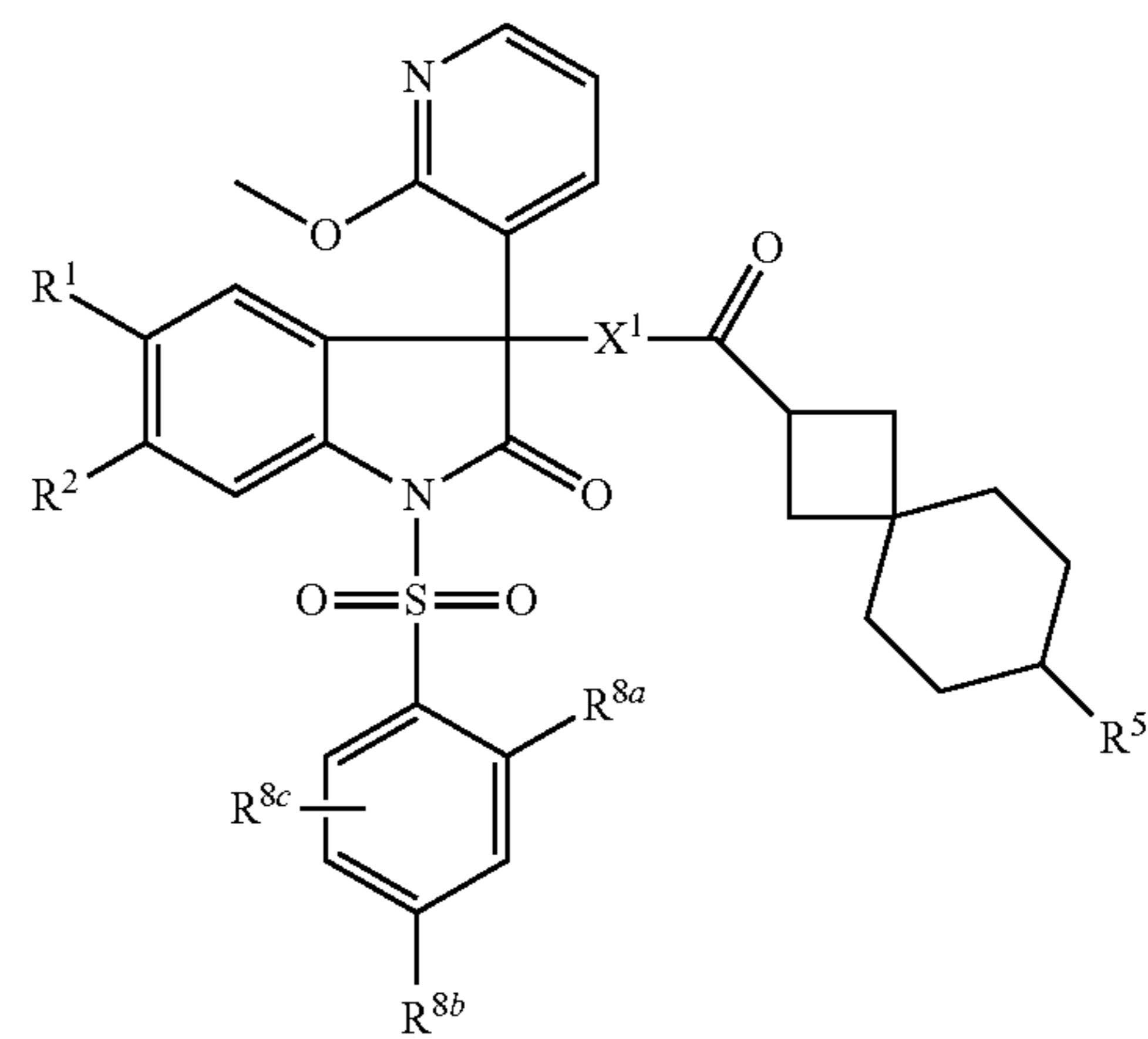
10

15

20

32

-continued



I.24

25

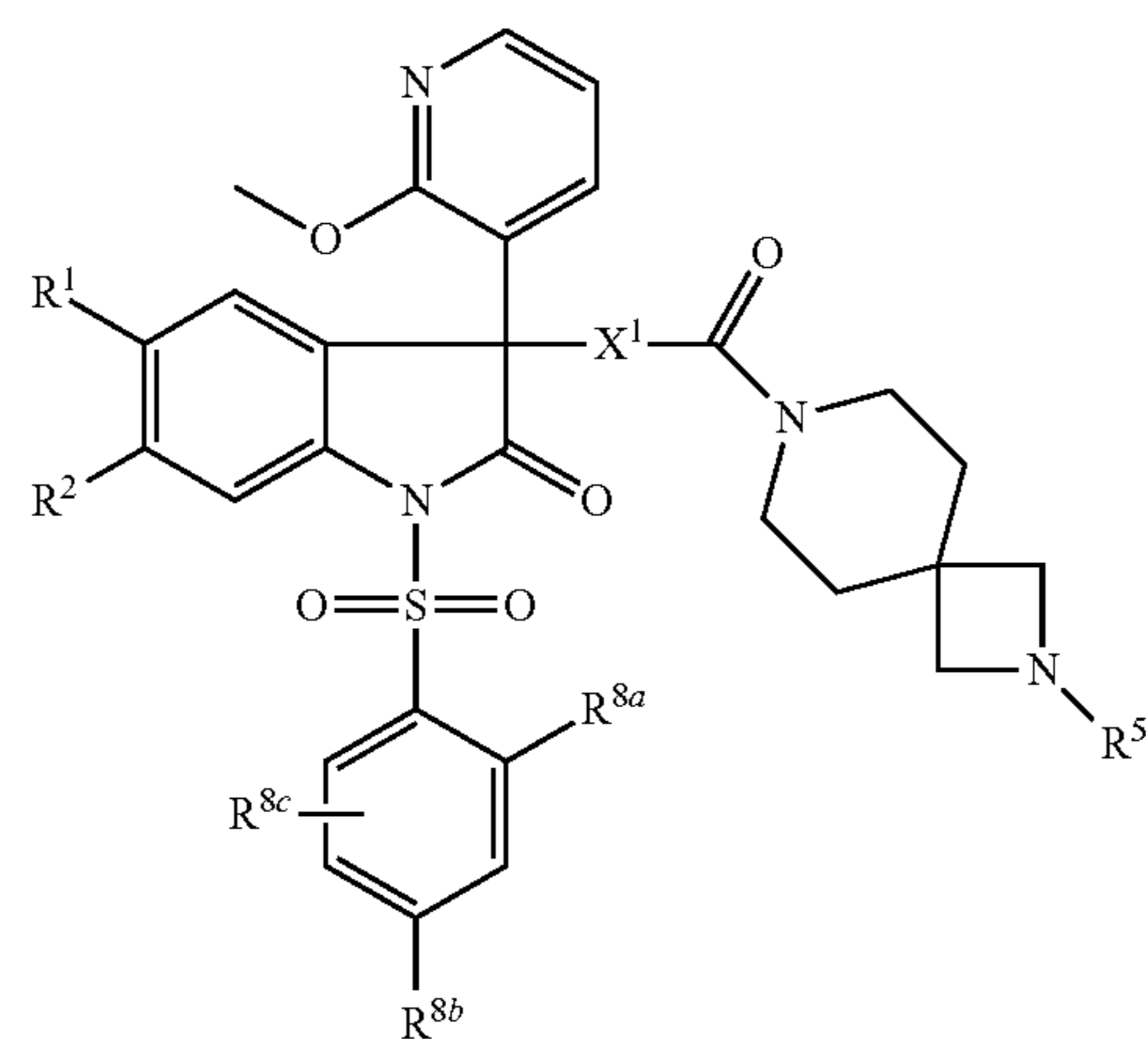
I.22

30

35

40

45



I.25

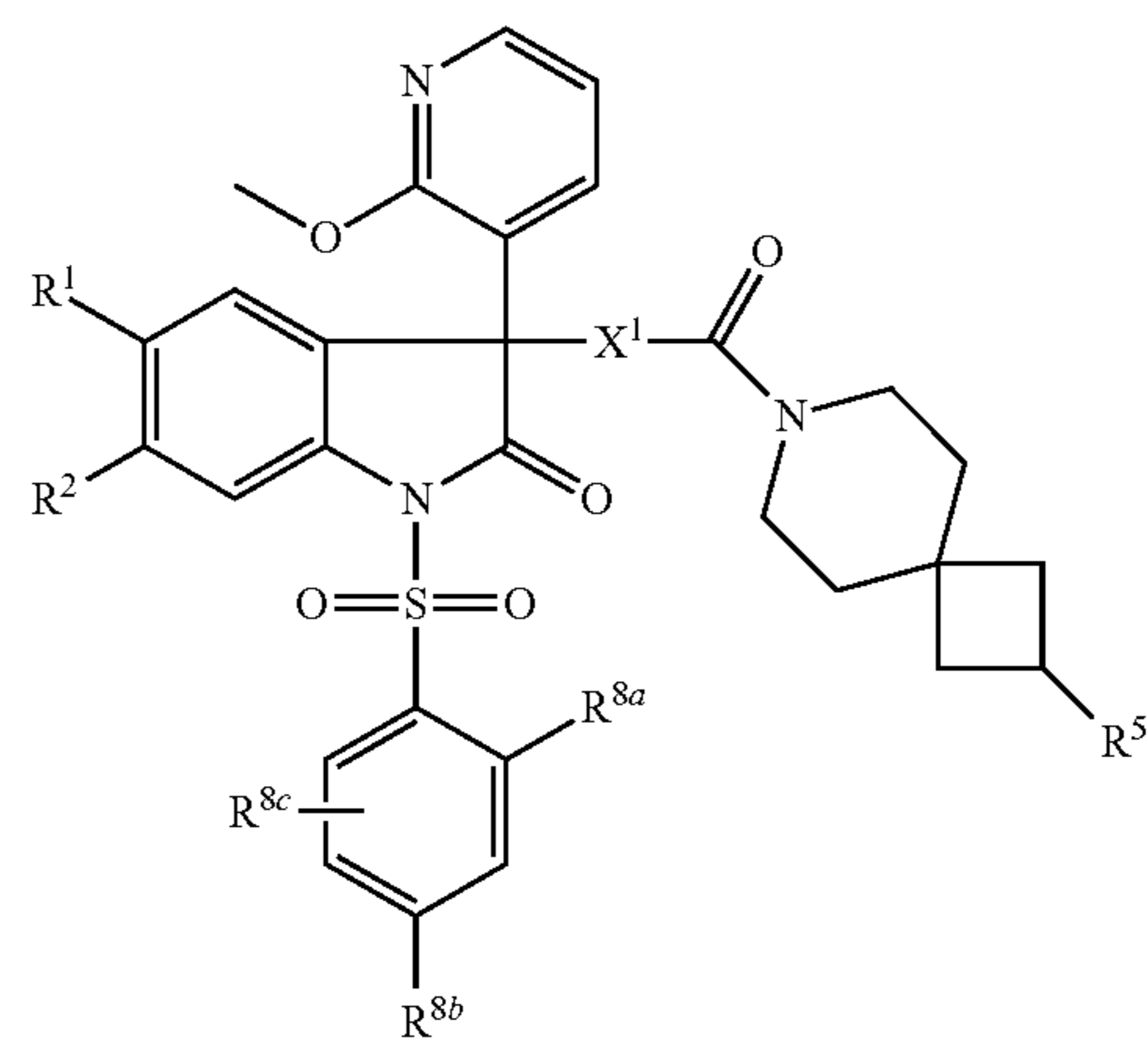
I.23

50

55

60

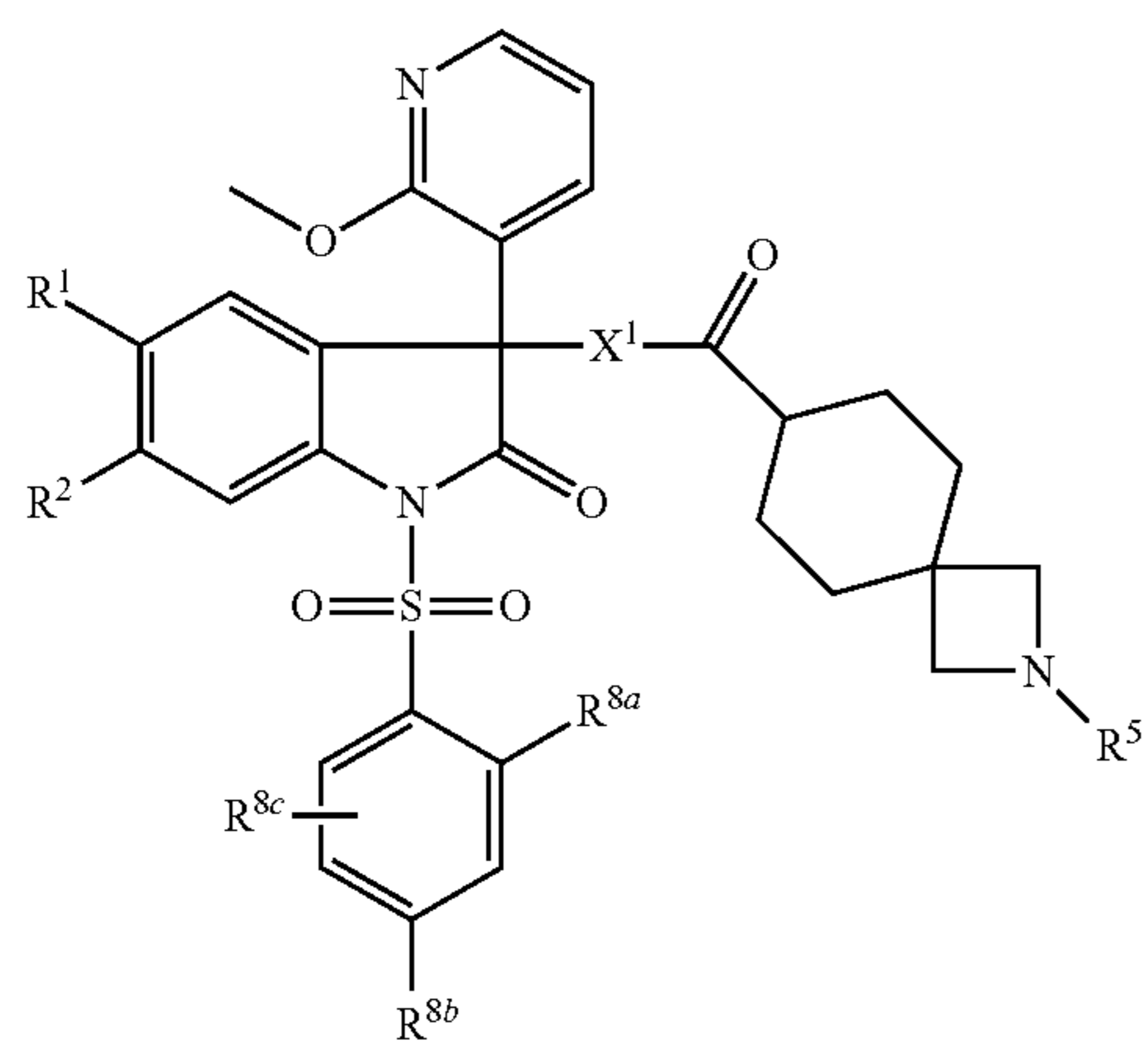
65



I.26

33

-continued



I.27

5

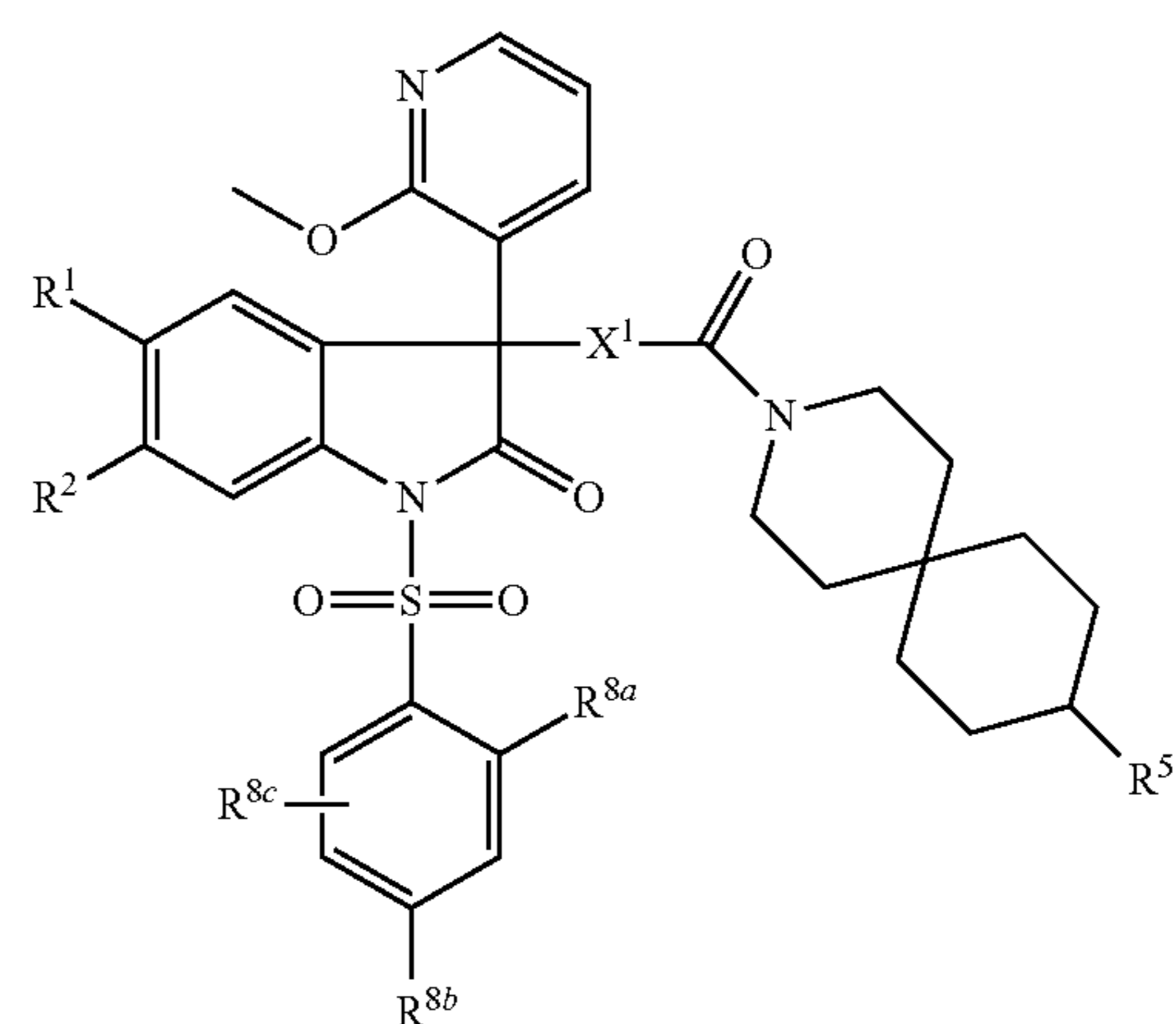
10

15

20

34

-continued



I.30

I.28

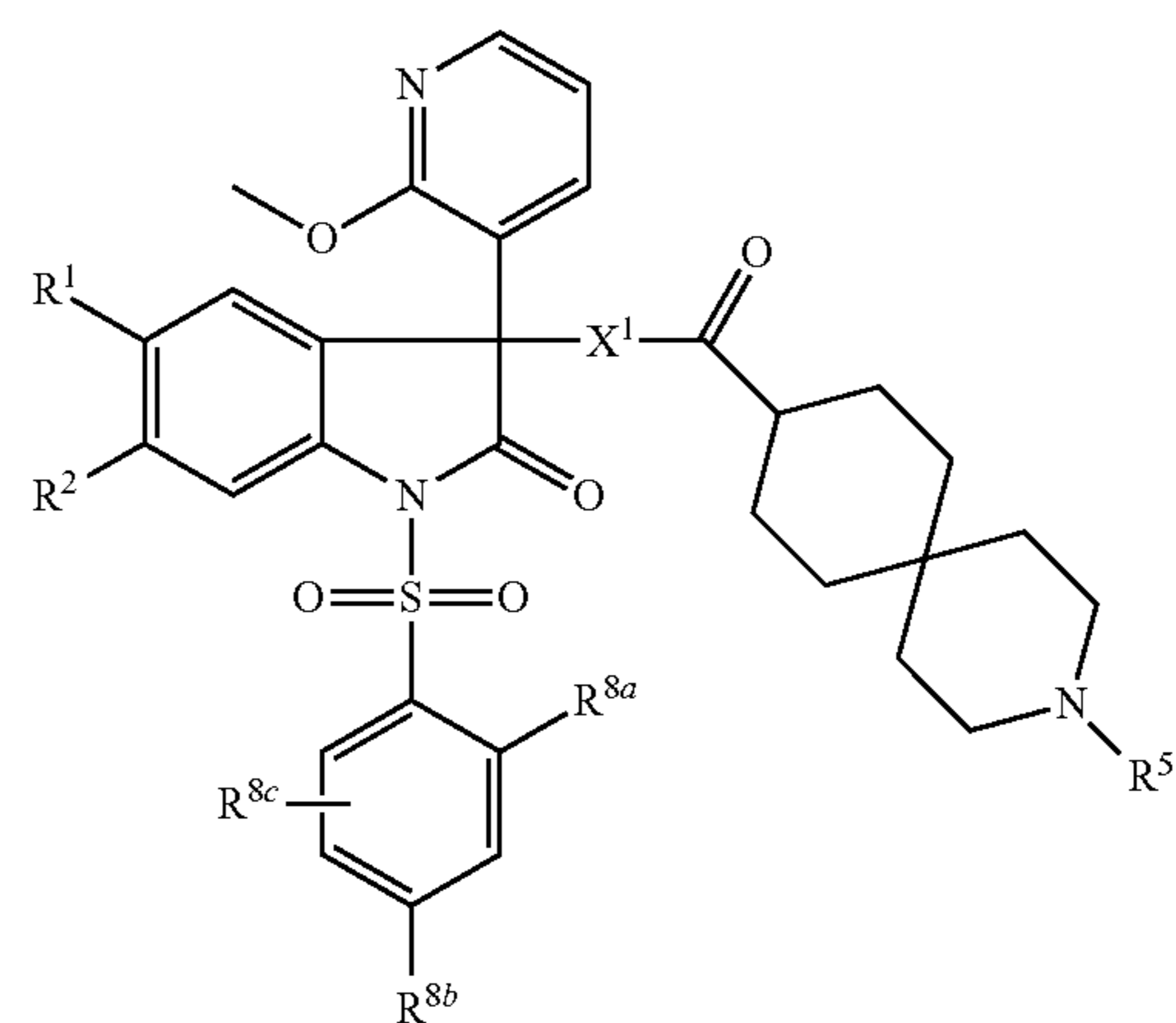
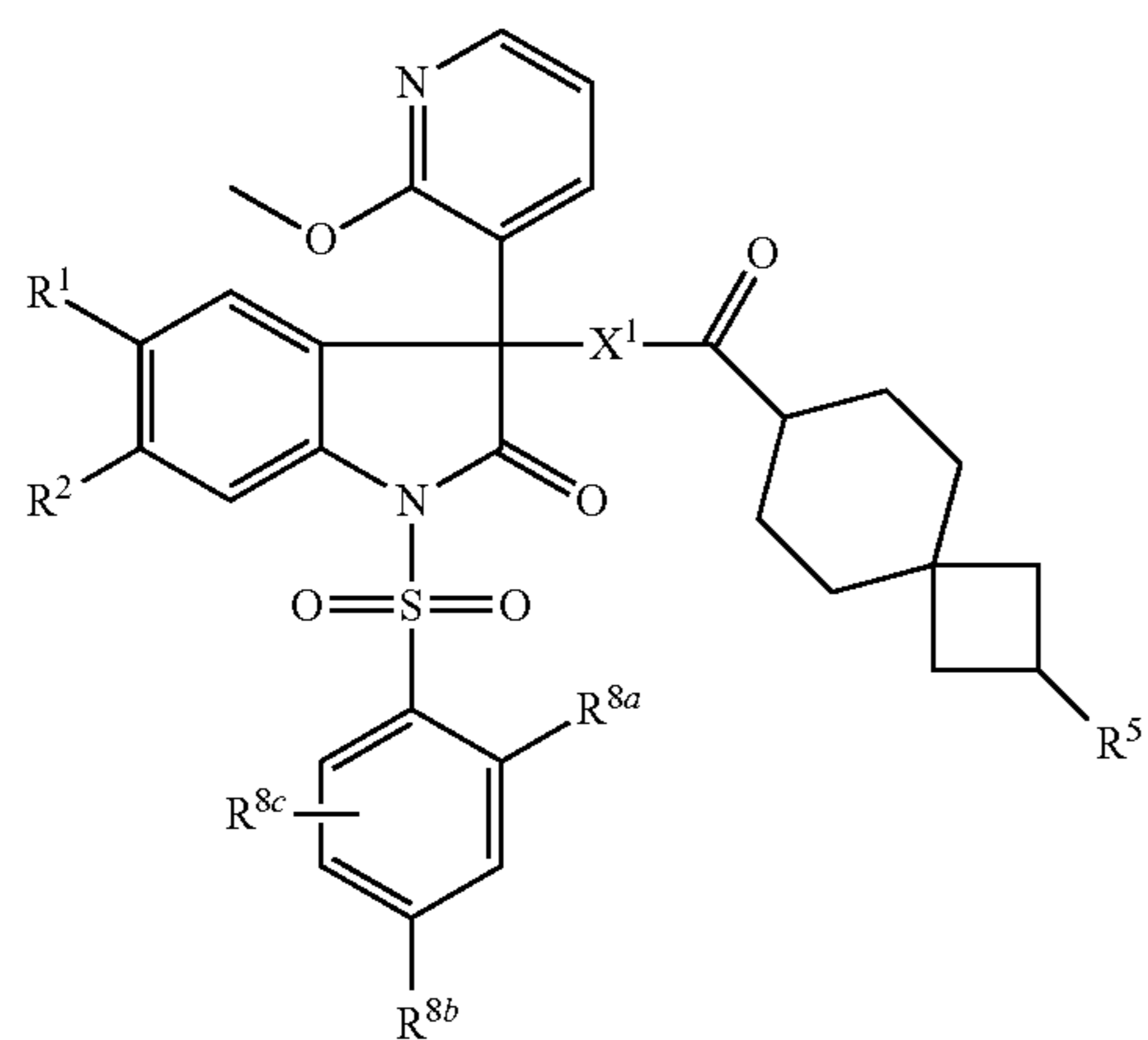
25

30

35

40

45



I.31

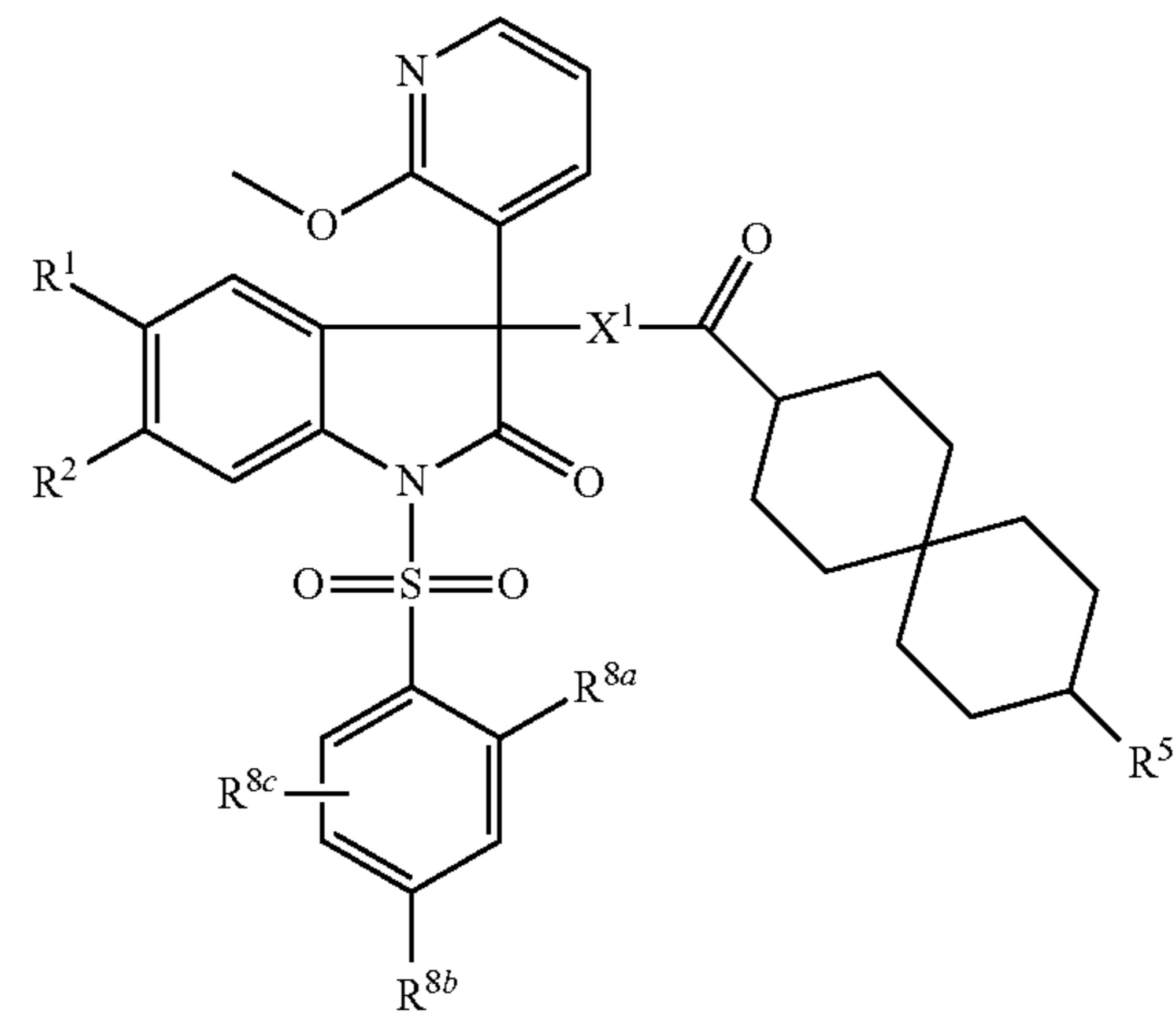
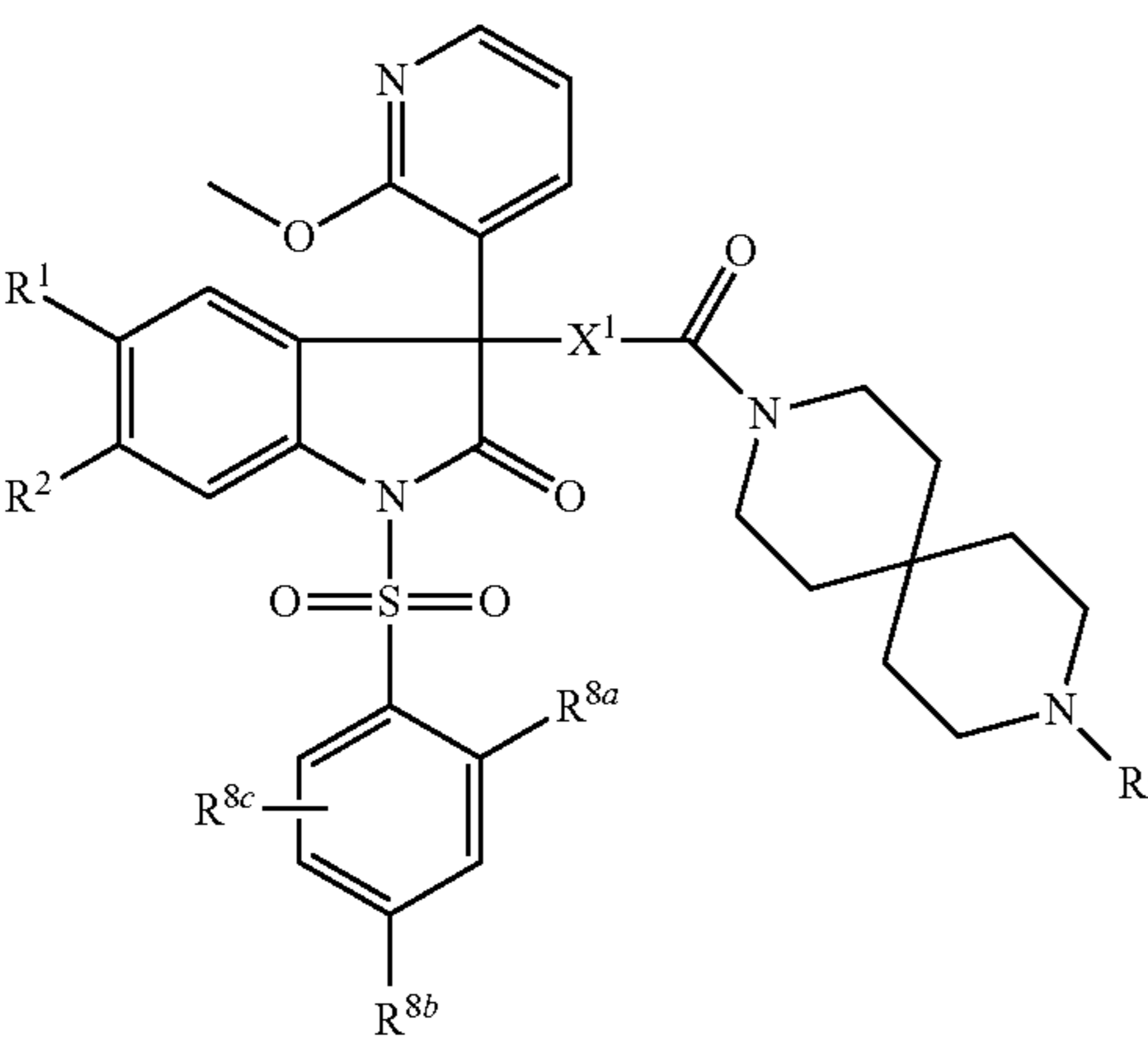
I.29

50

55

60

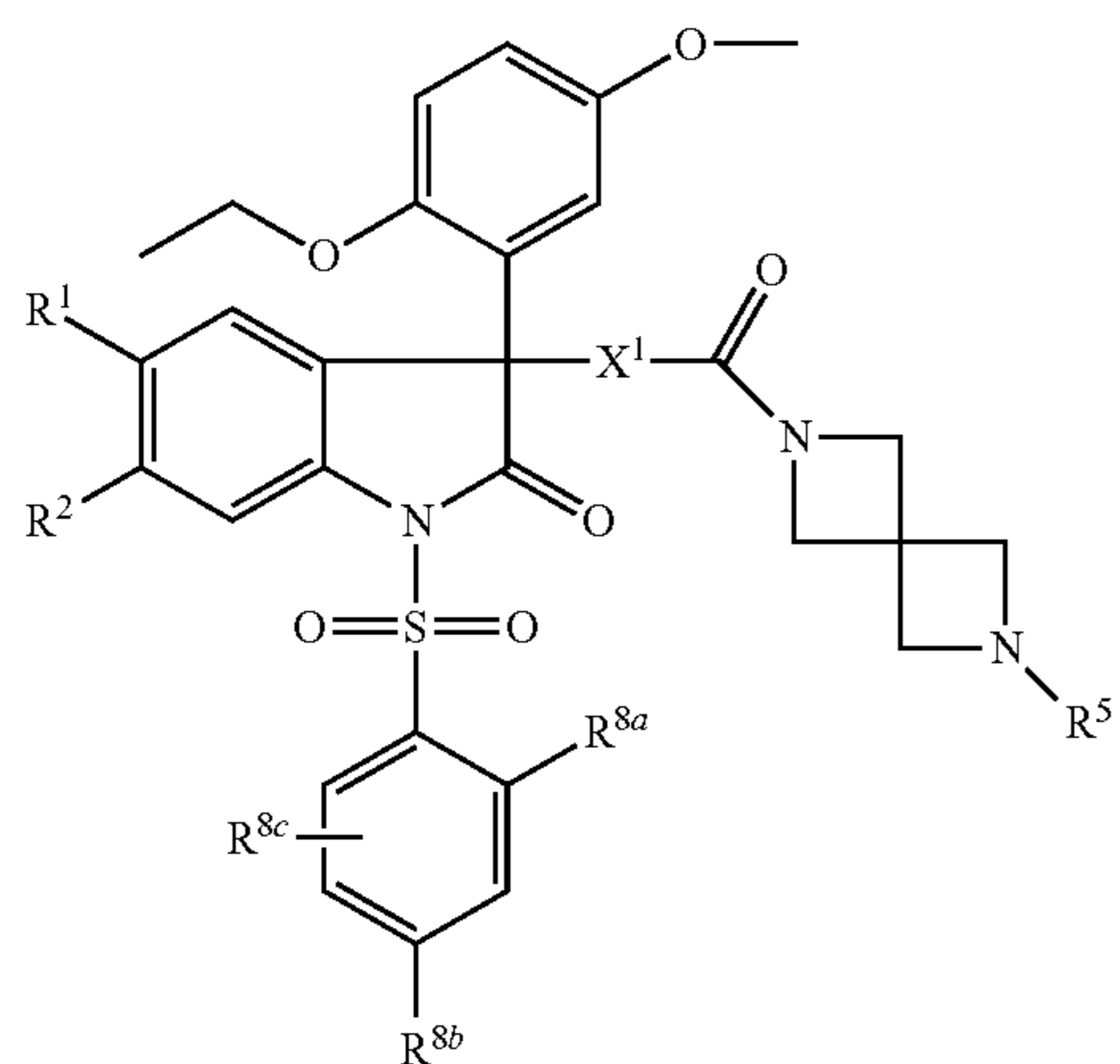
65



I.32

35

-continued



I.33

5

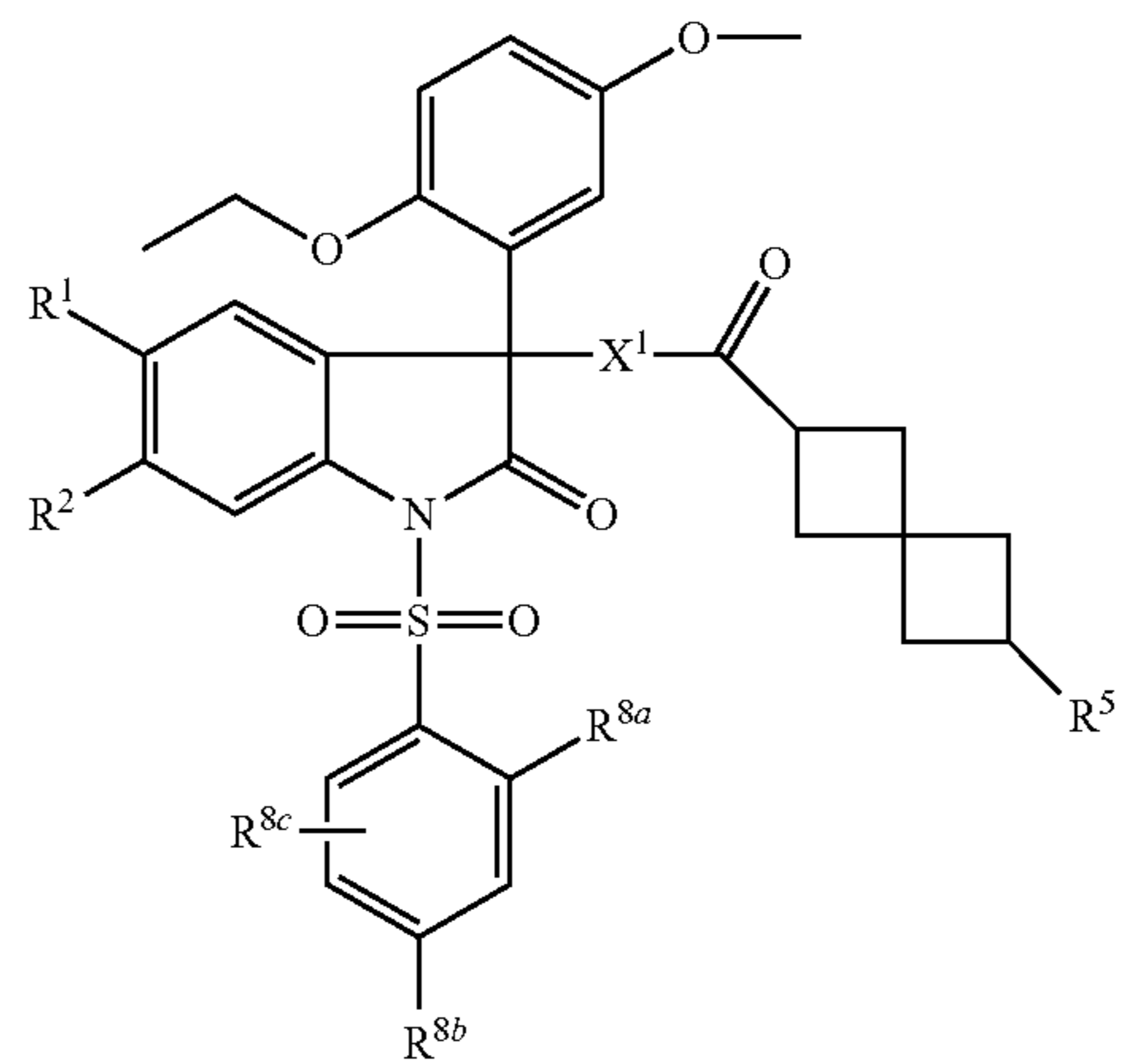
10

15

20

36

-continued



I.36

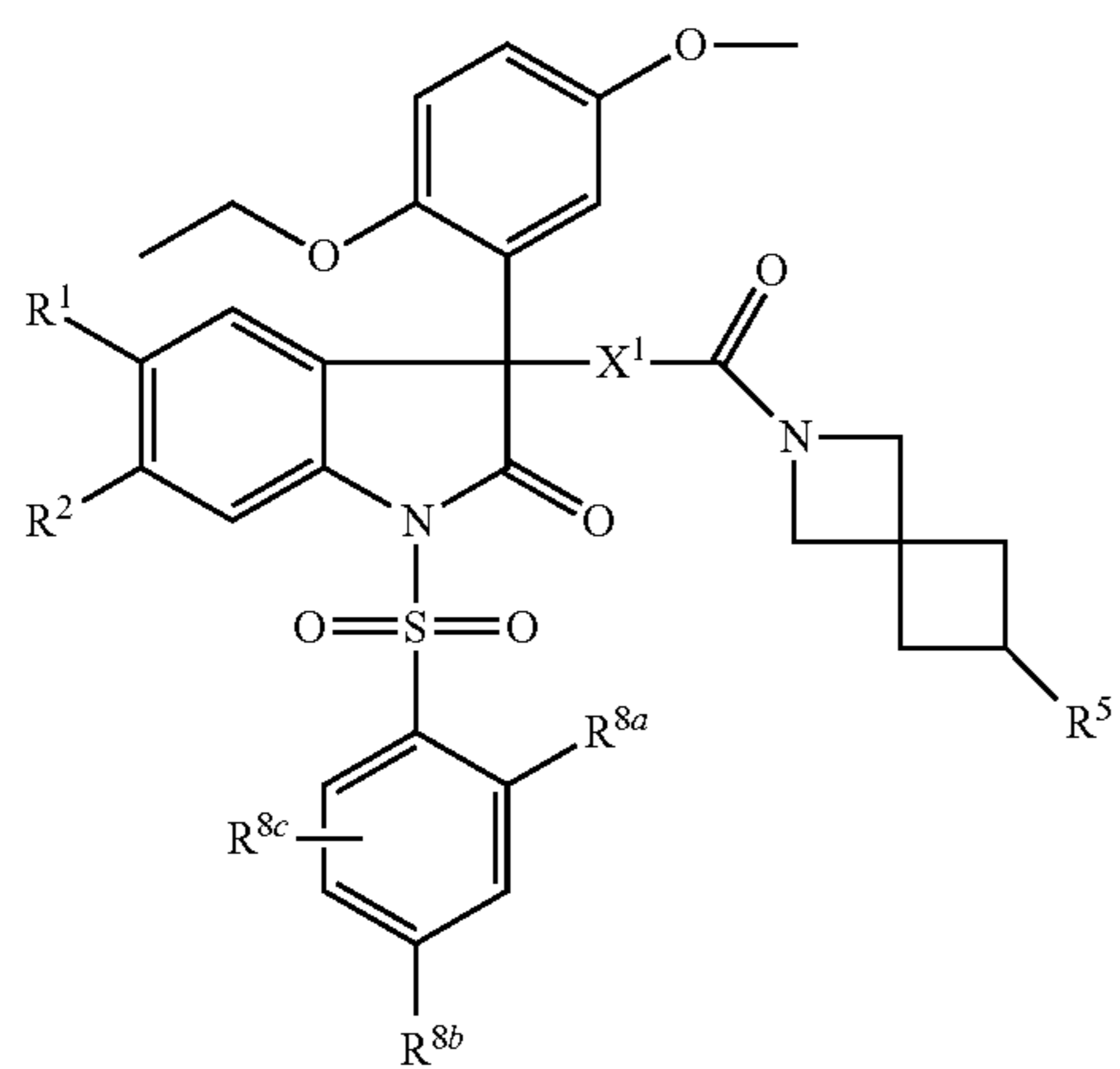
I.34 25

30

35

40

45



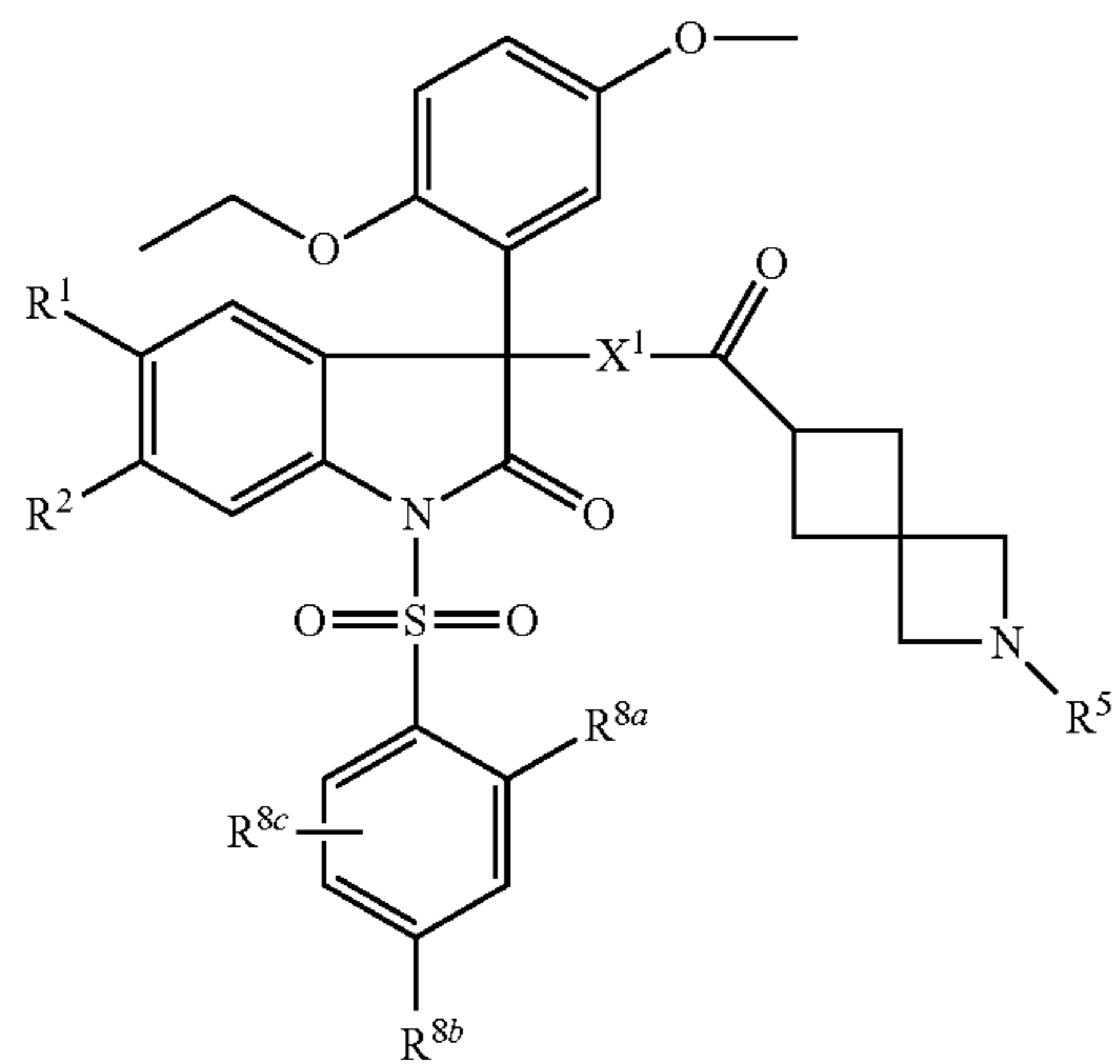
I.37

I.35 50

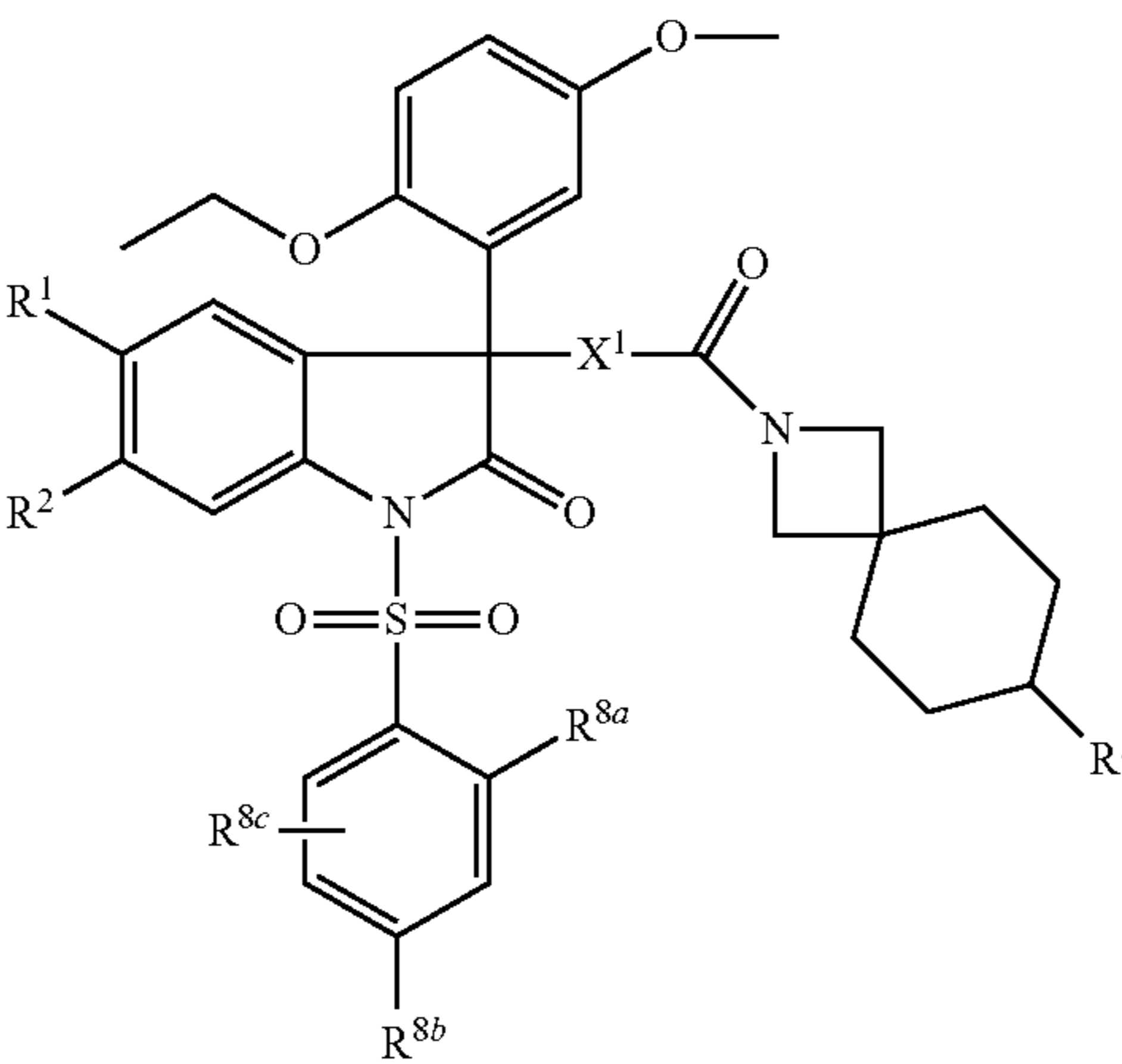
55

60

65

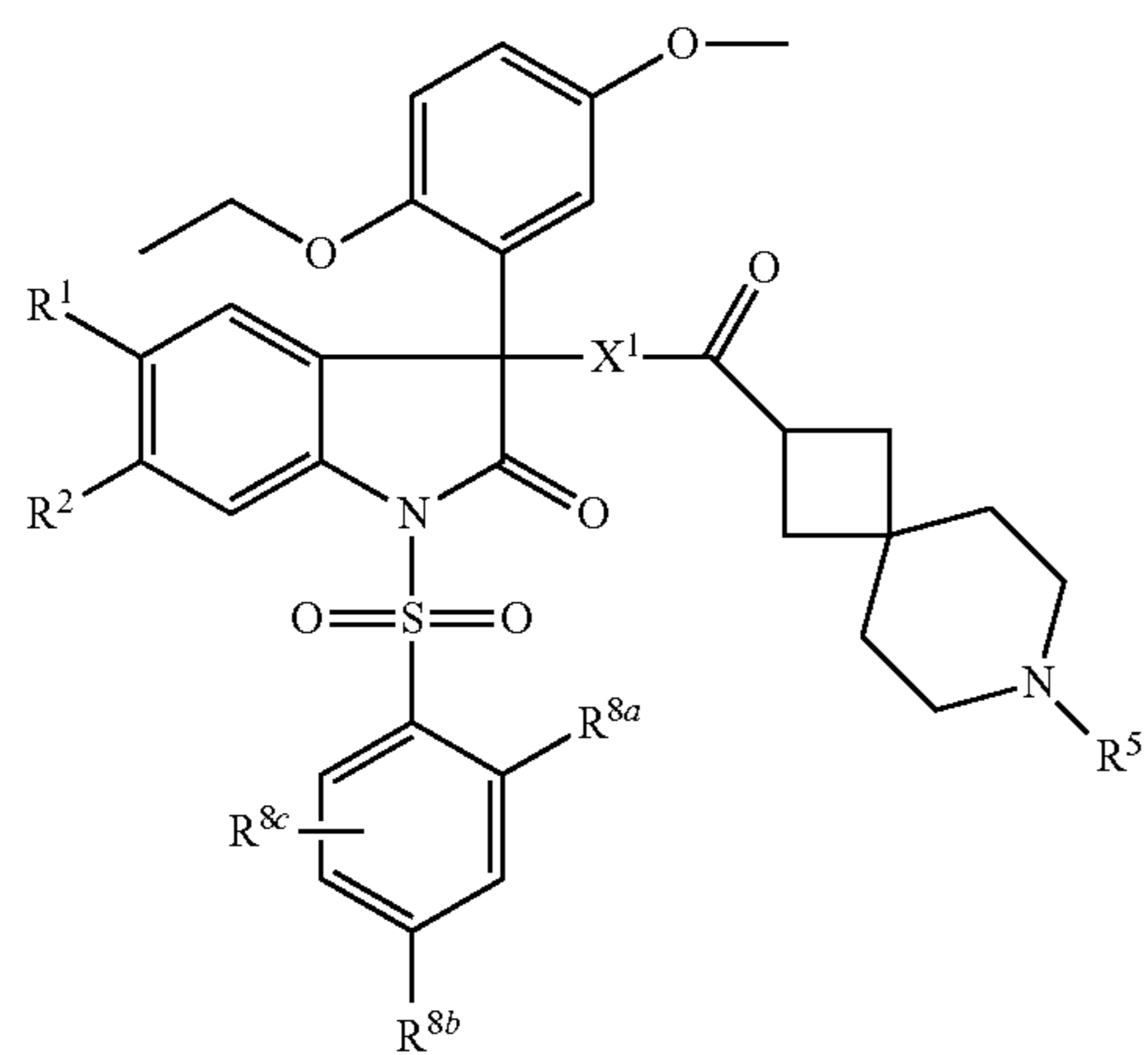


I.38



37

-continued



I.39

5

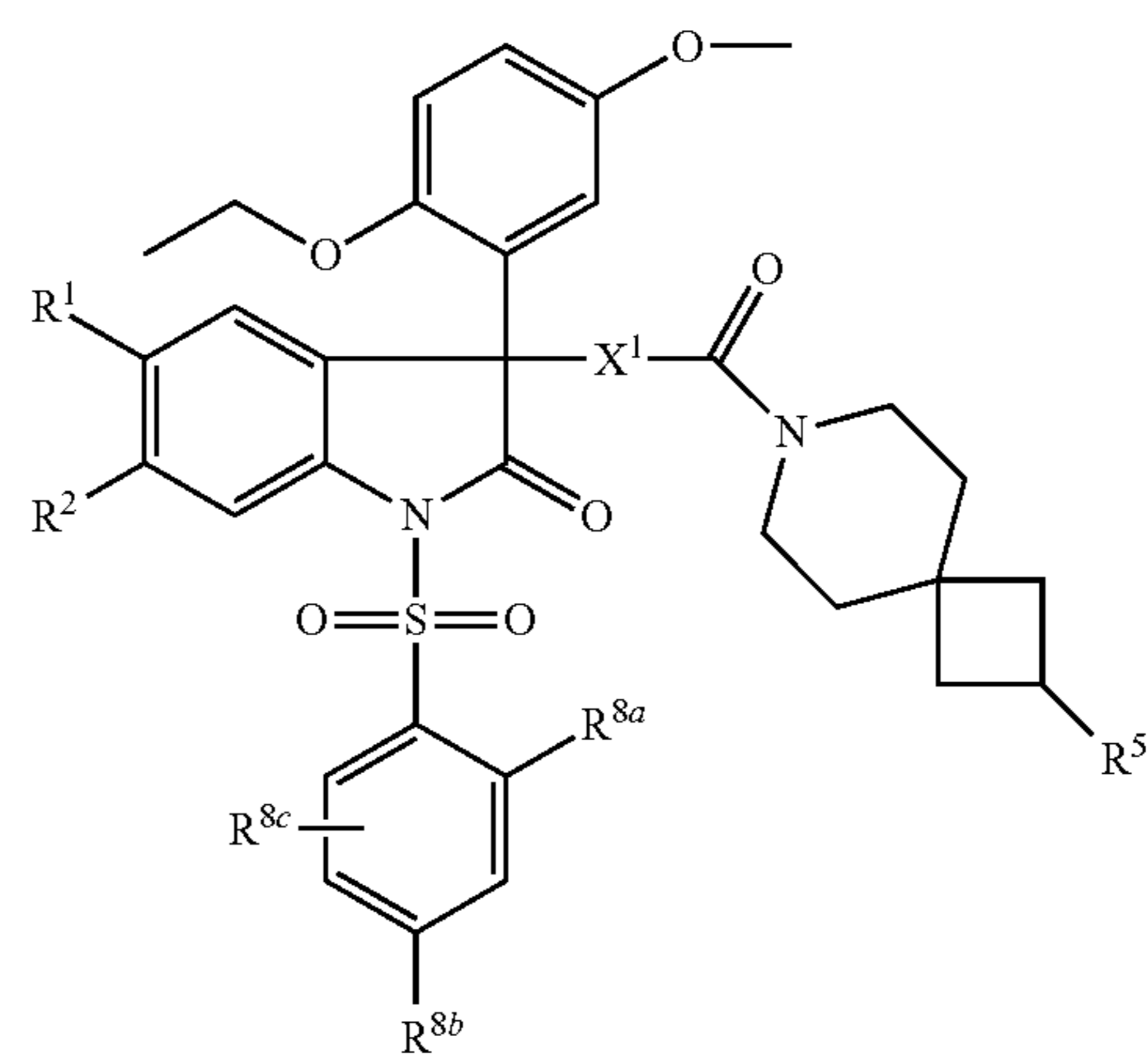
10

15

20

38

-continued



I.42

I.40

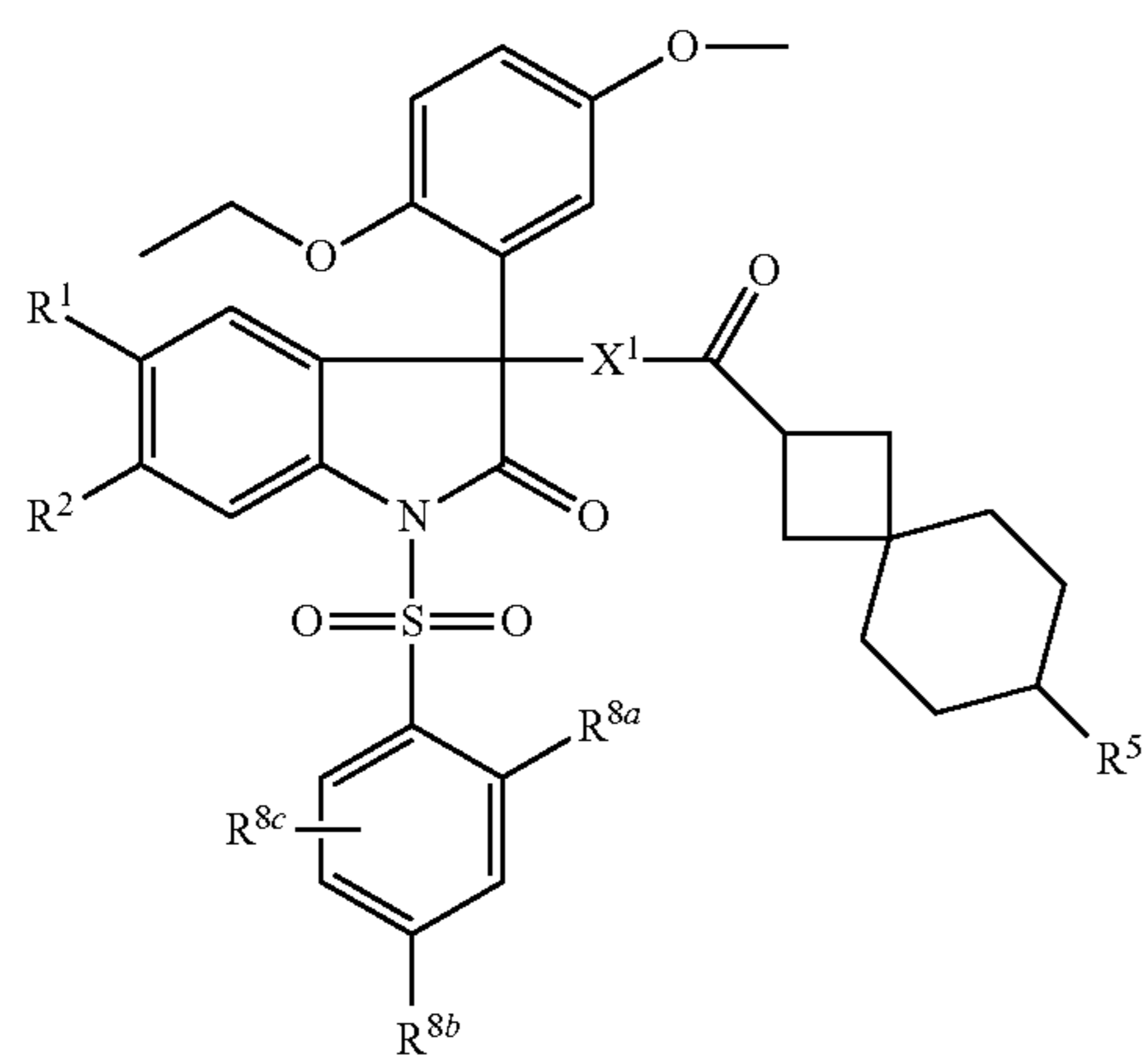
25

30

35

40

45



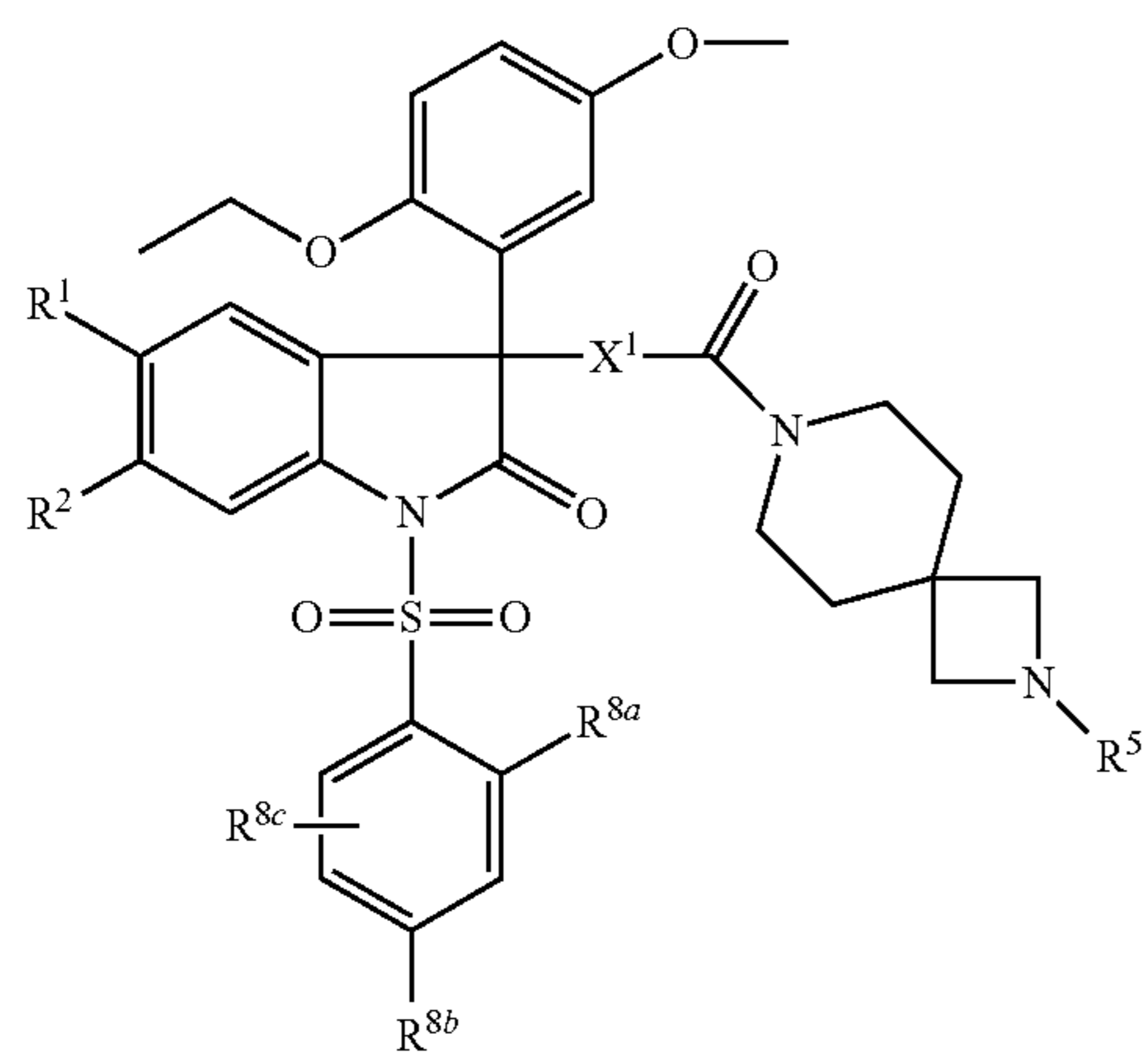
I.41

50

55

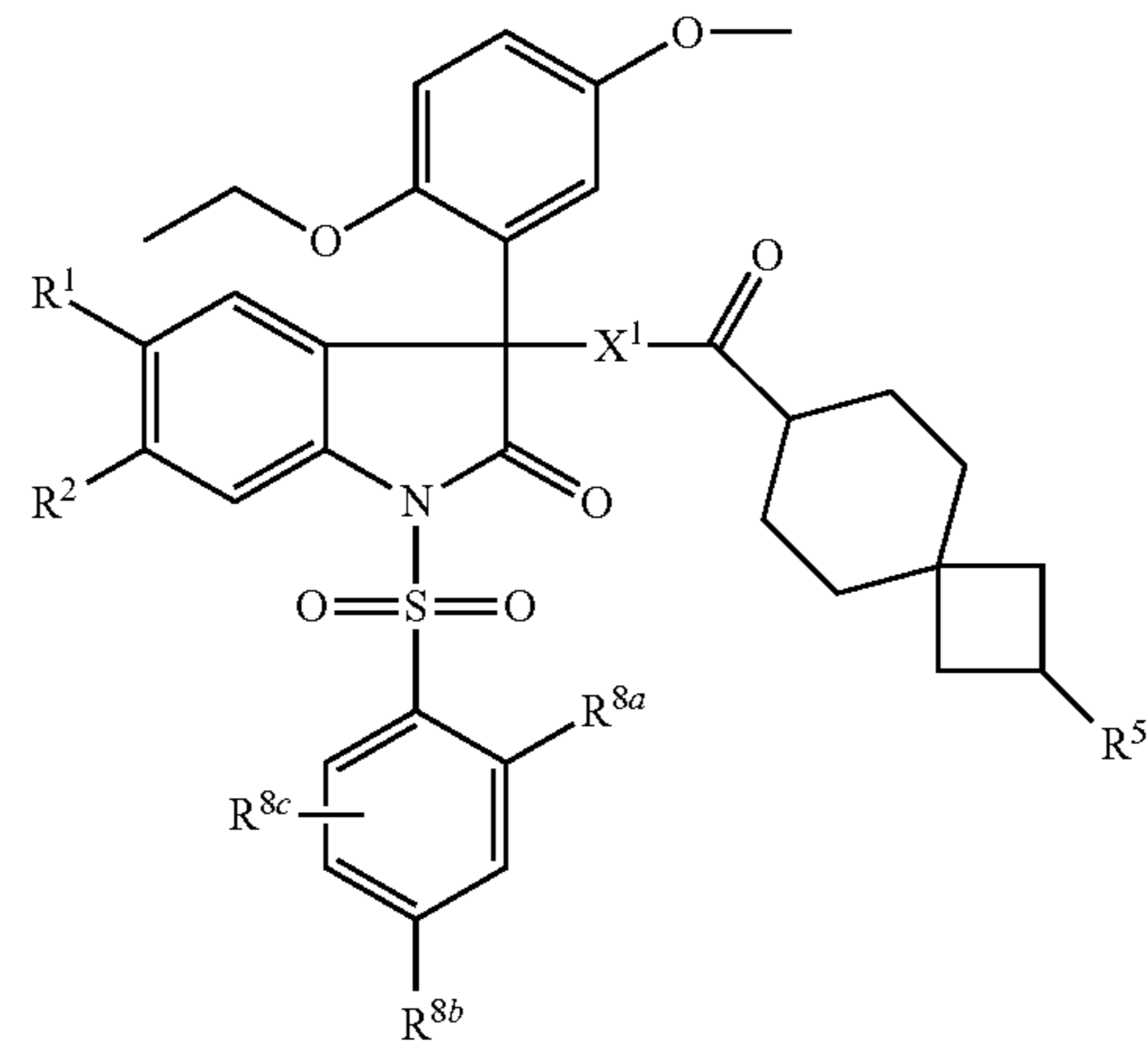
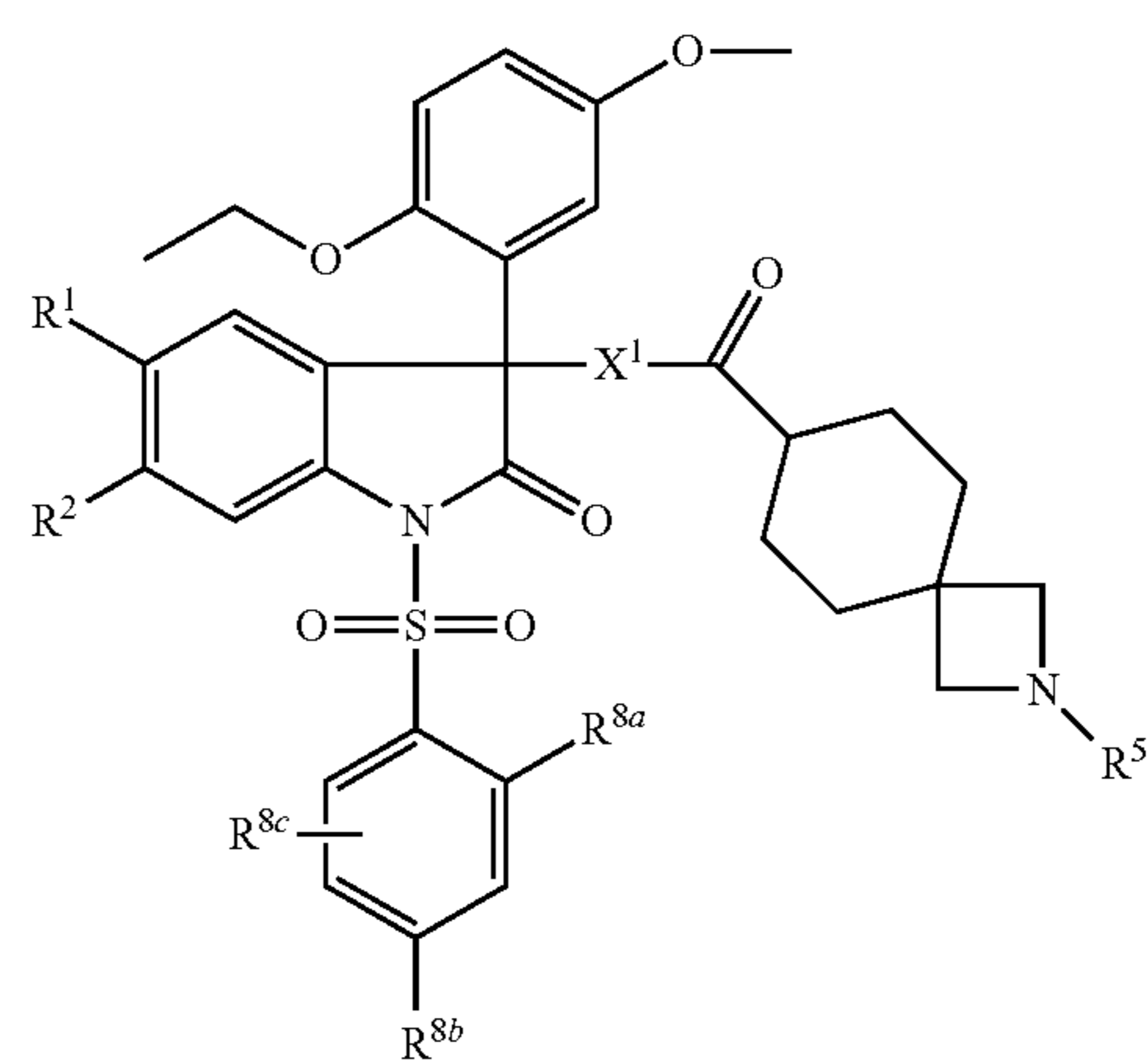
60

65



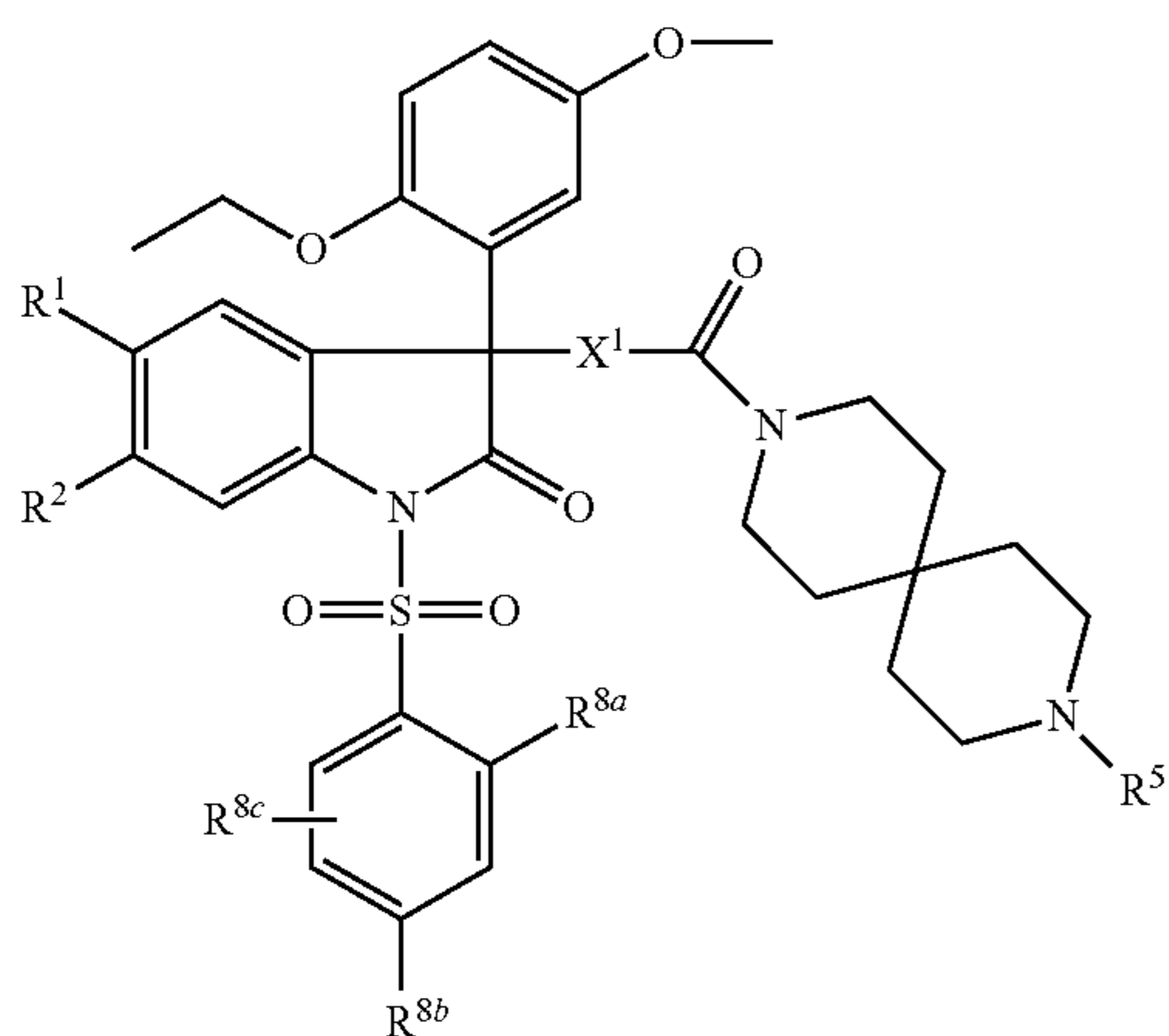
I.43

I.44



39

-continued



I.45

5

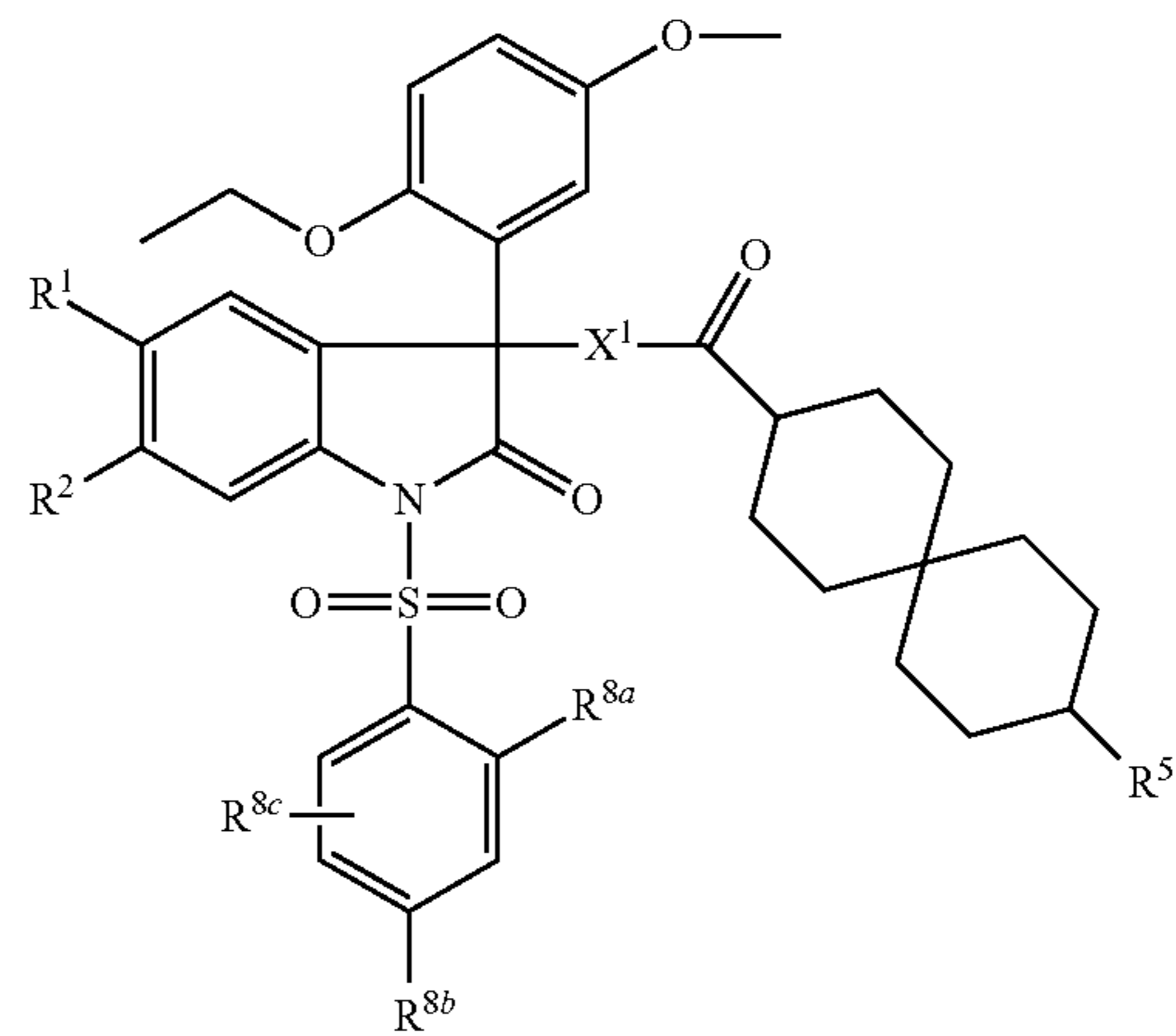
10

15

20

40

-continued



I.48

I.46

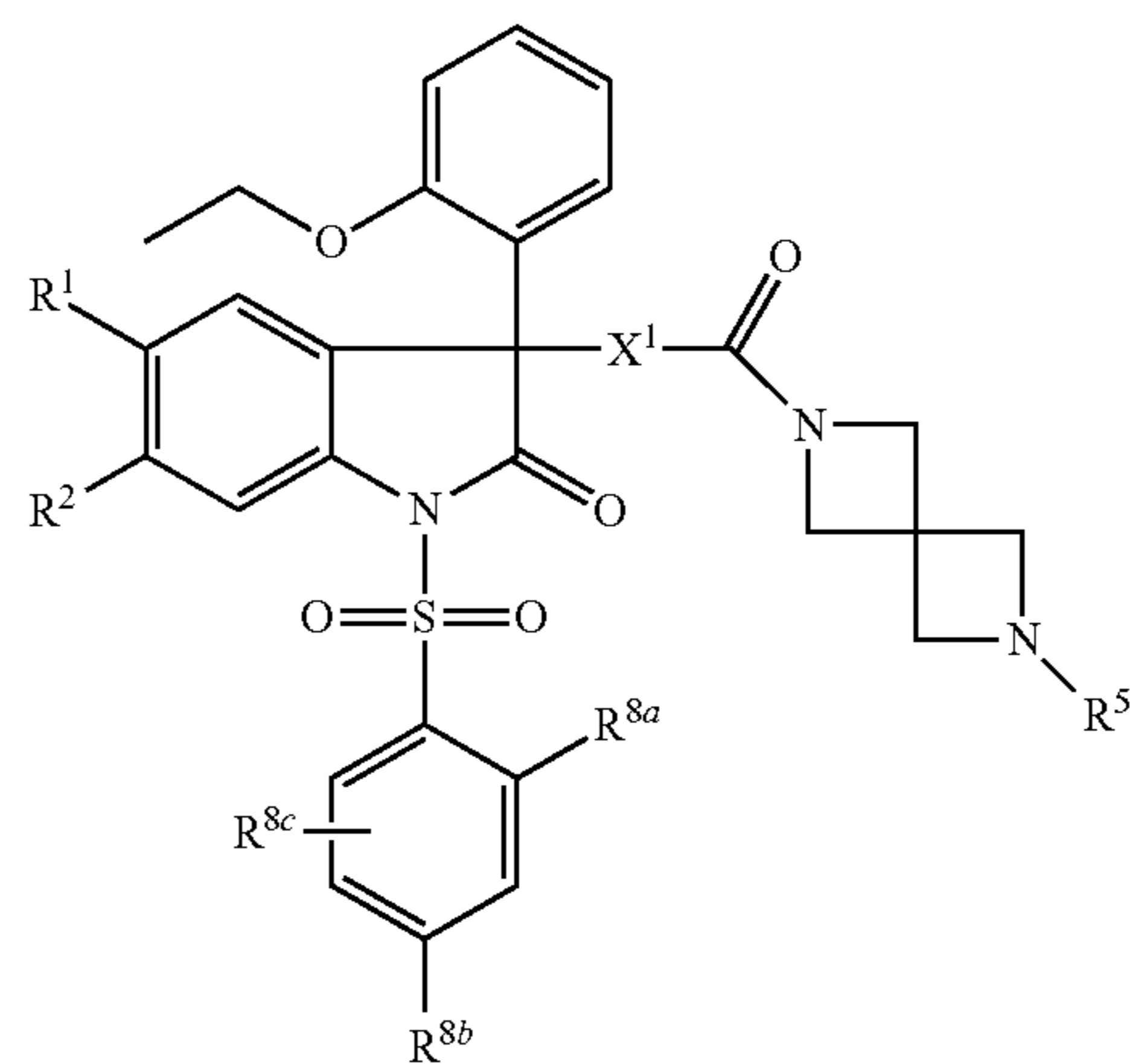
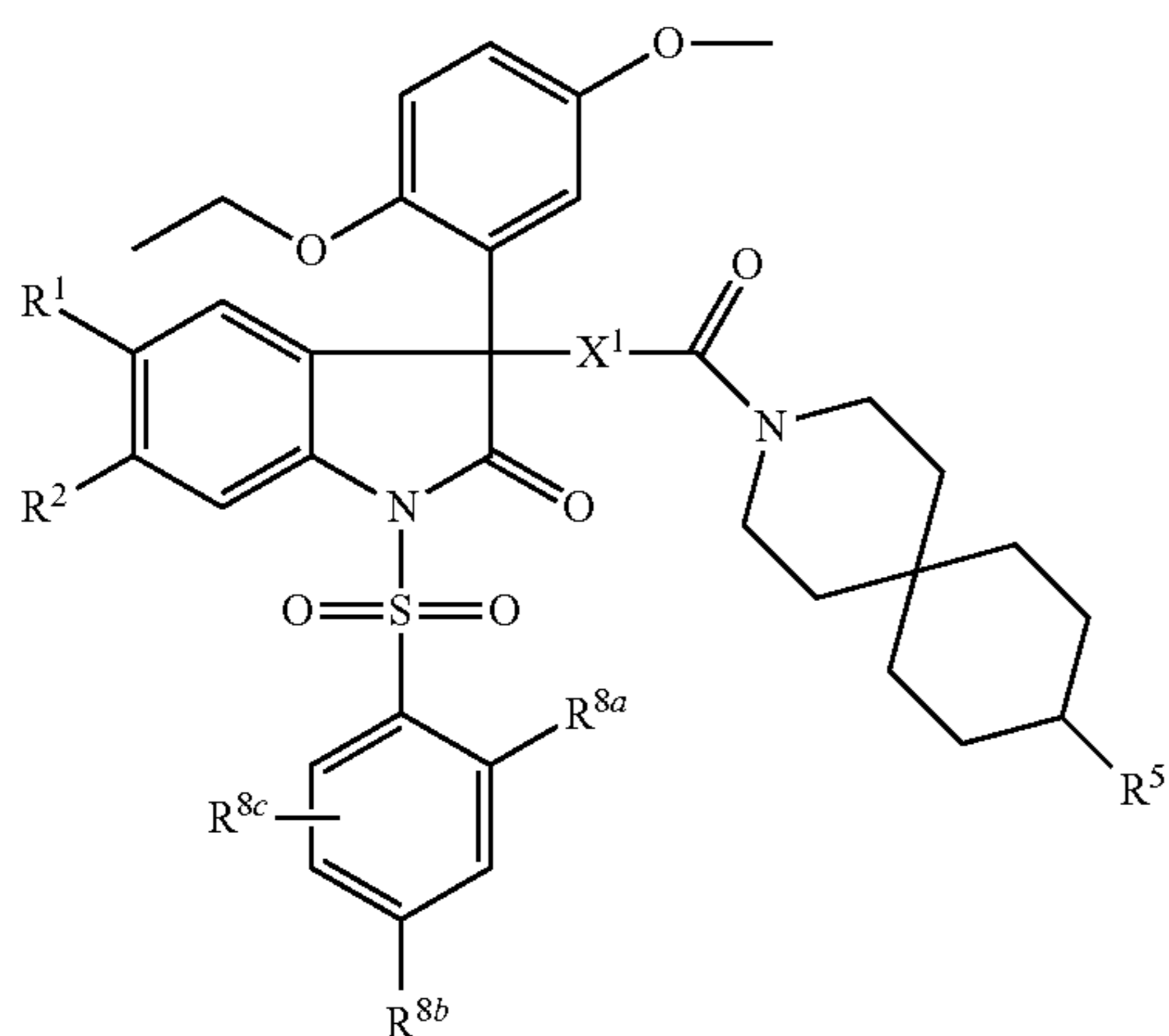
25

30

35

40

45



I.49

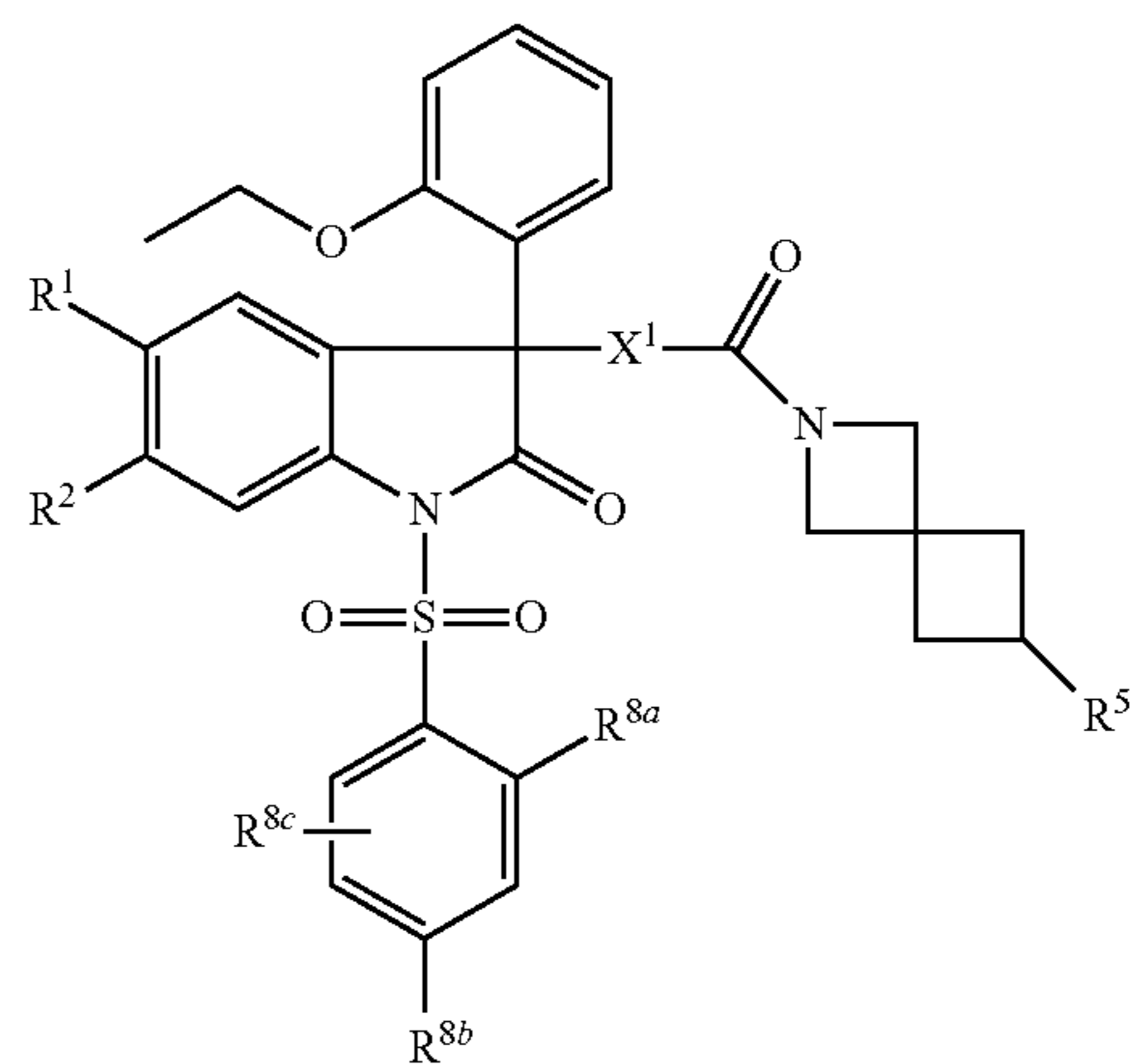
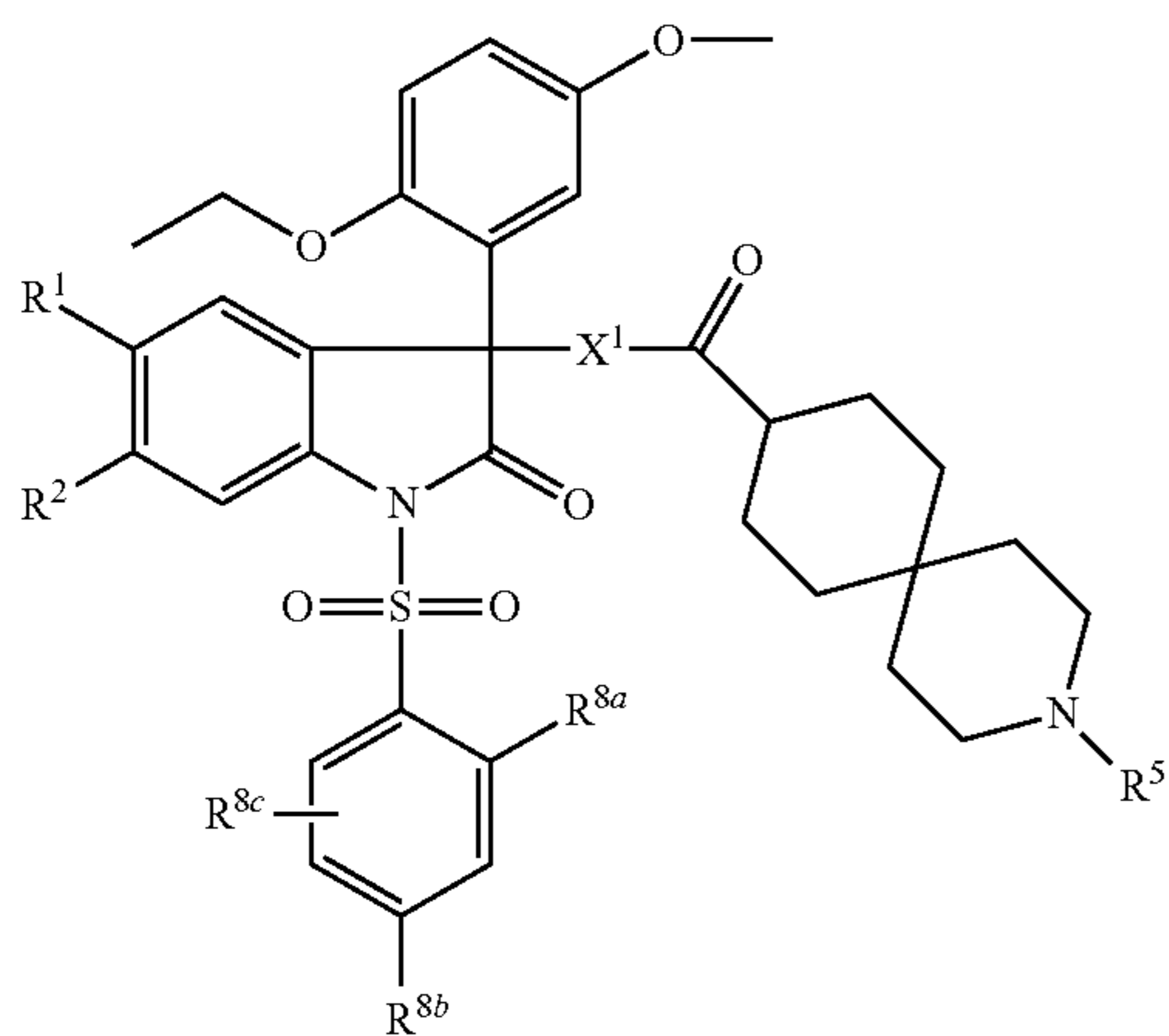
I.47

50

55

60

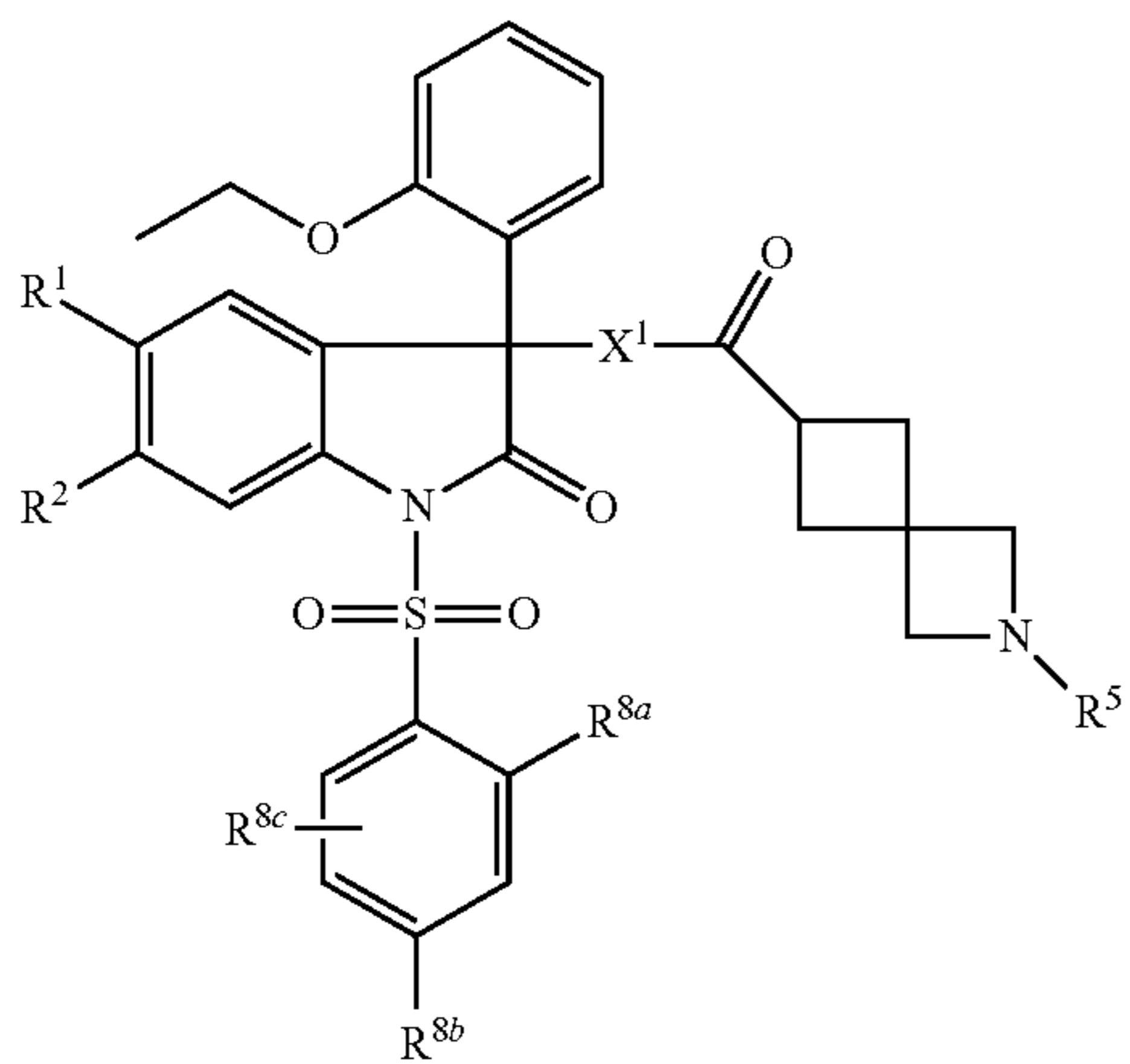
65



I.50

41

-continued



I.51

5

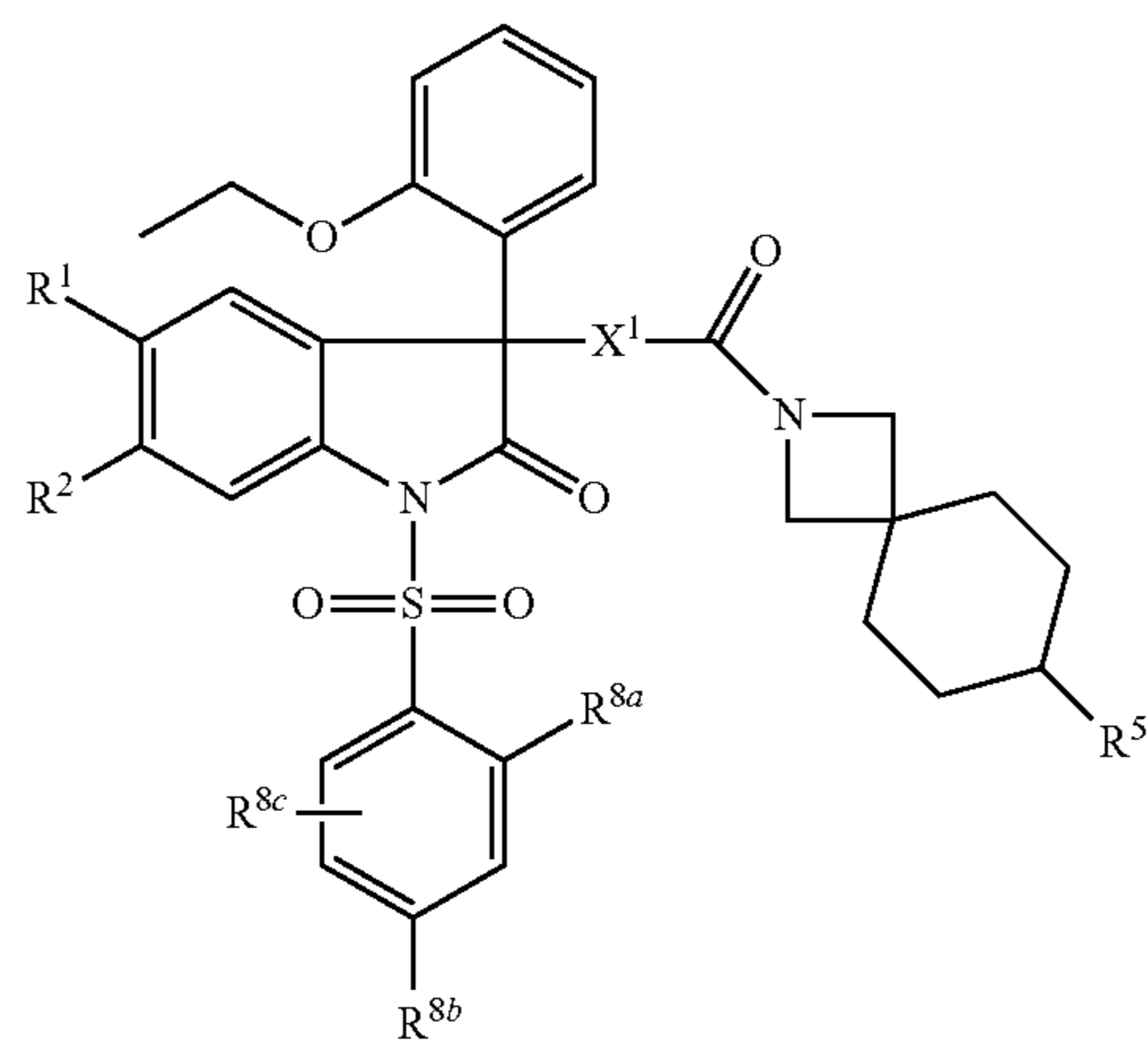
10

15

20

42

-continued



I.54

I.52

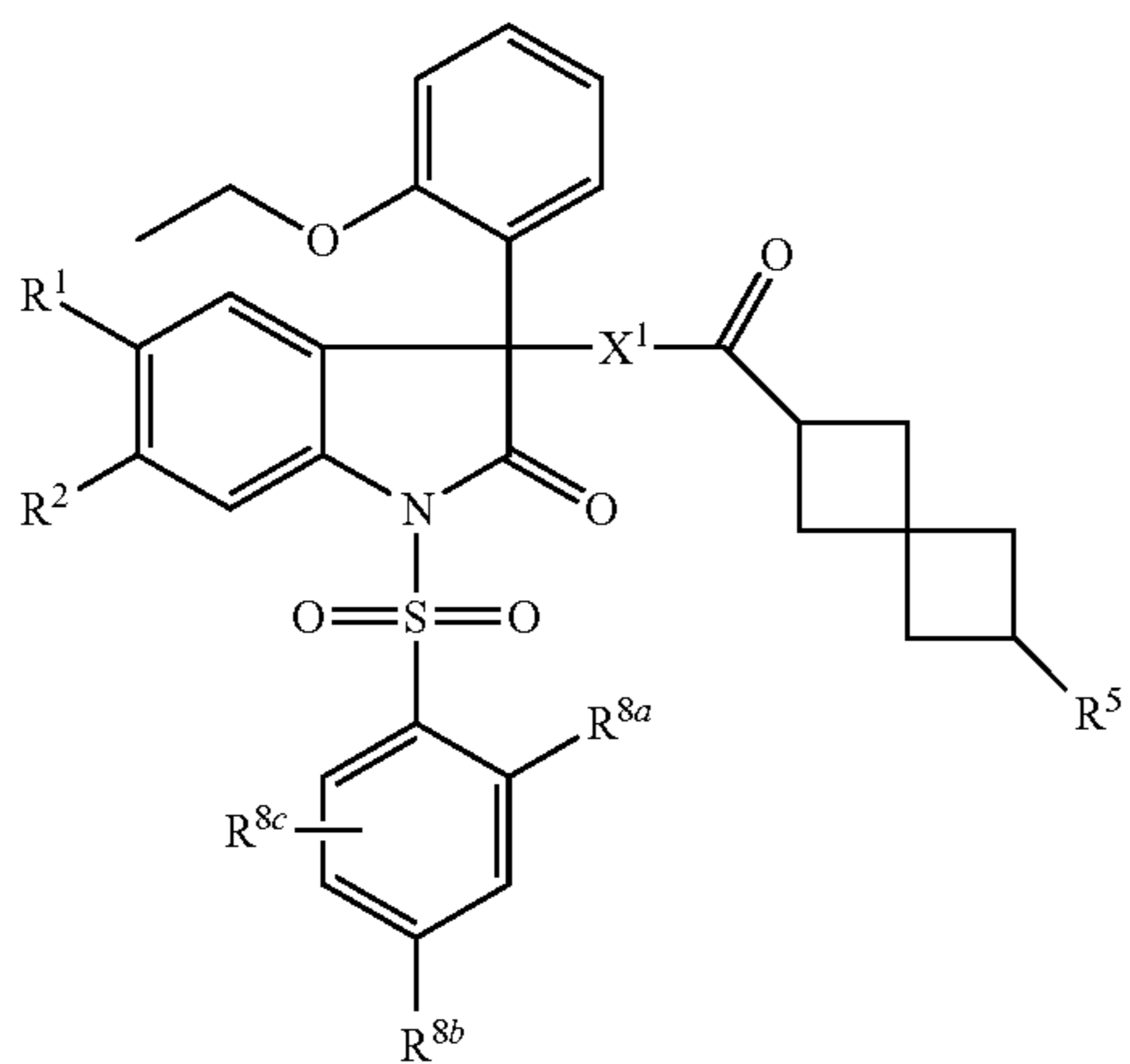
25

30

35

40

45



I.55

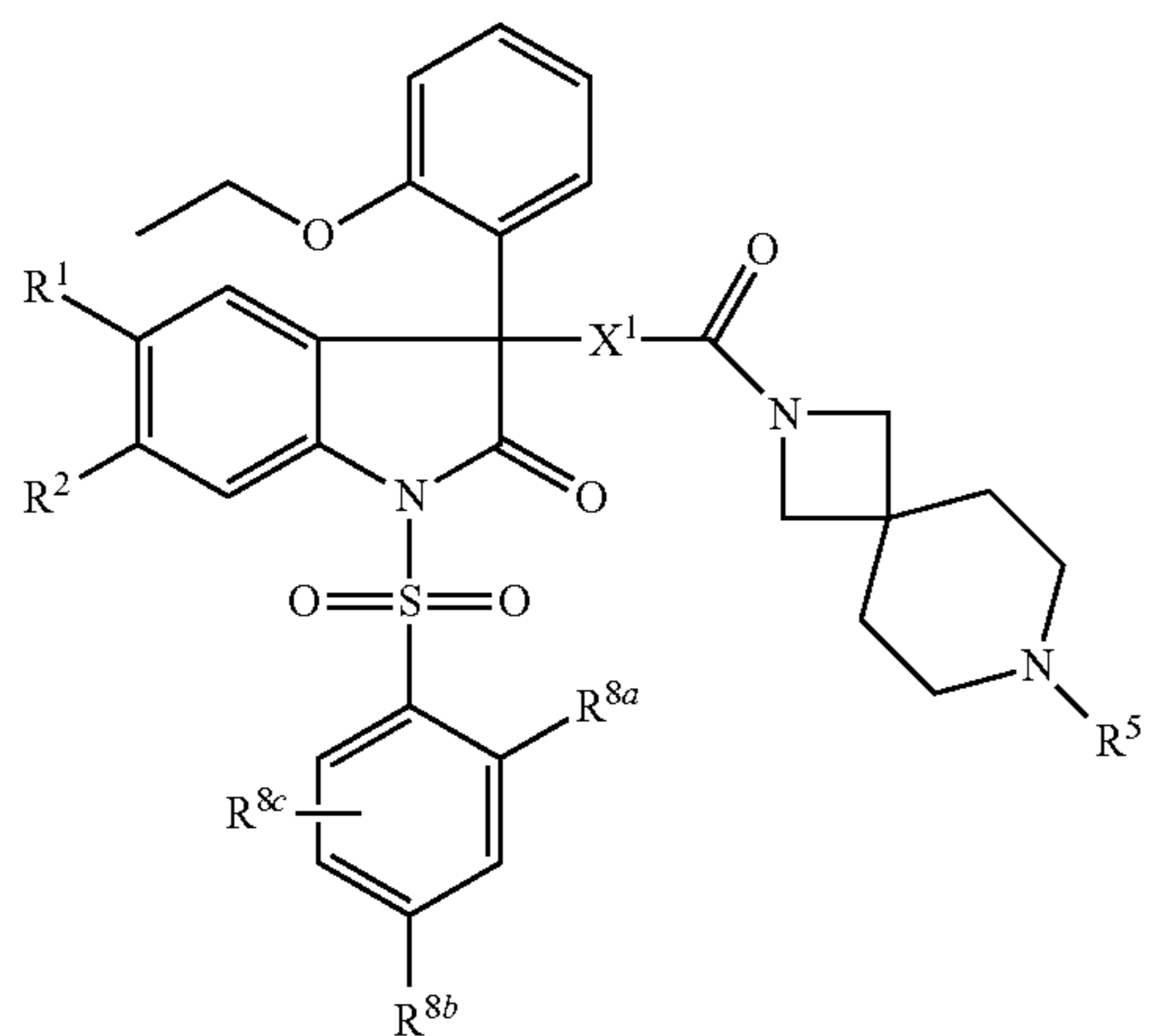
I.53

50

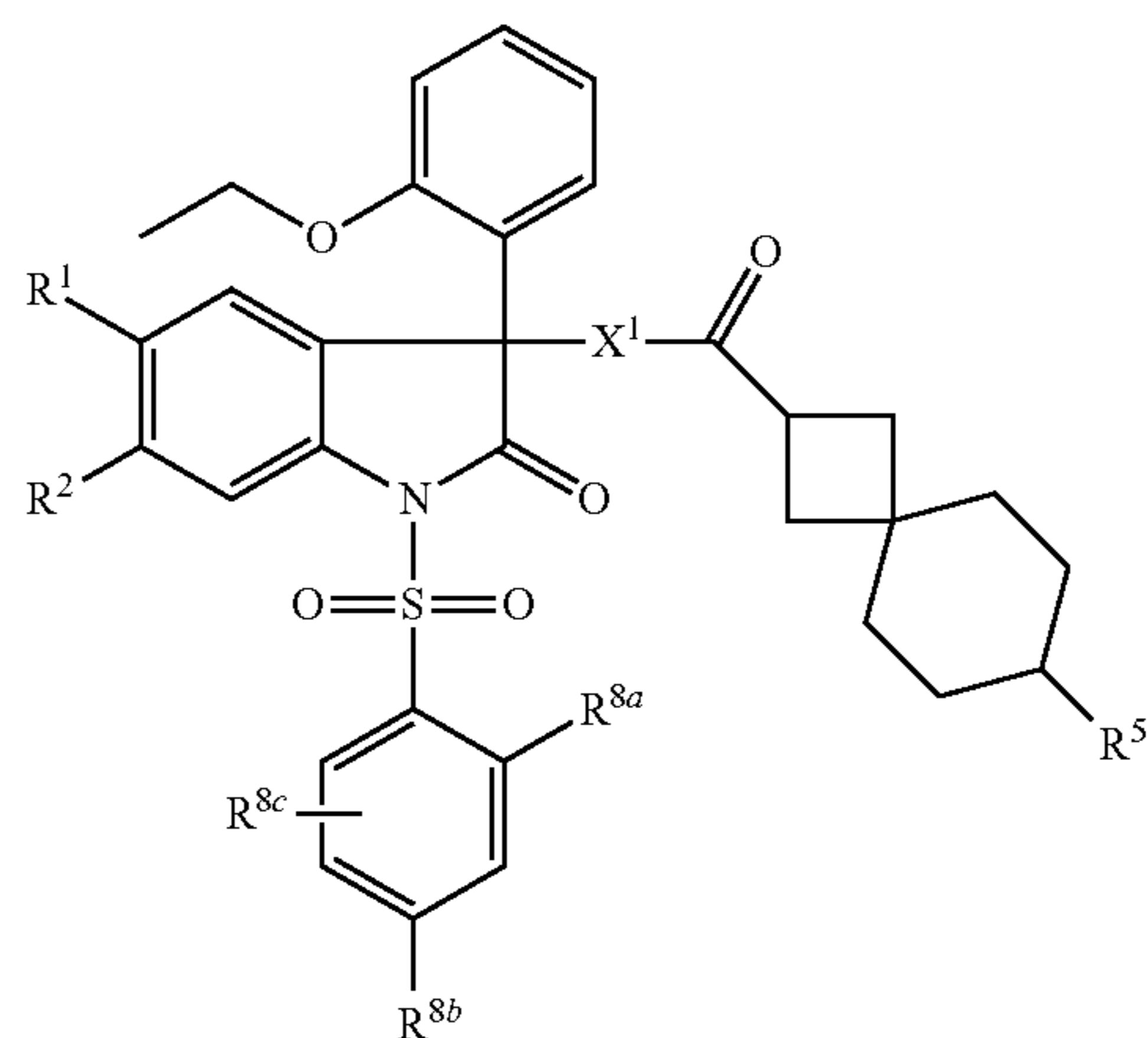
55

60

65

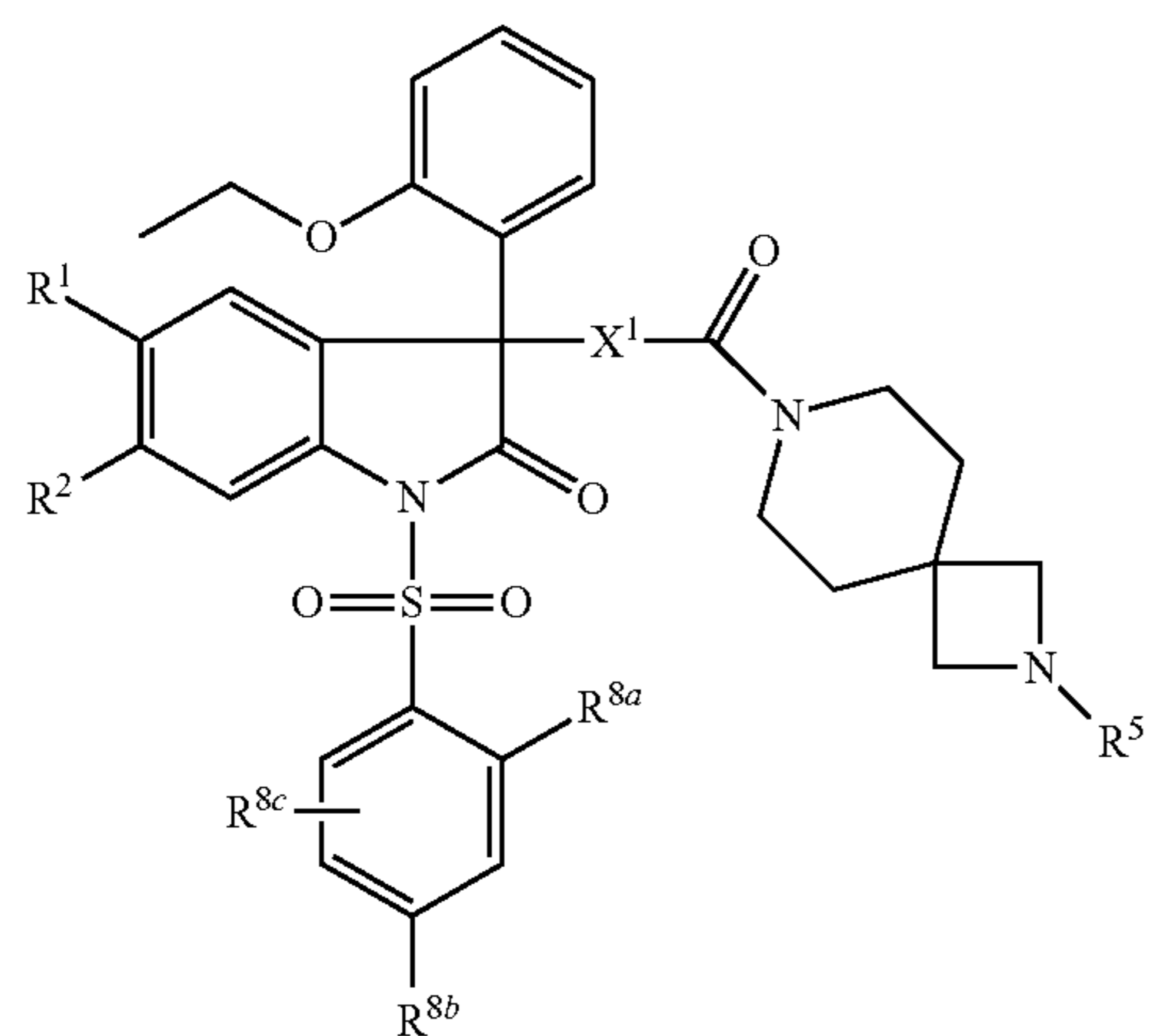


I.56



43

-continued



I.57

5

10

15

20

25

I.58

30

35

40

45

I.59

50

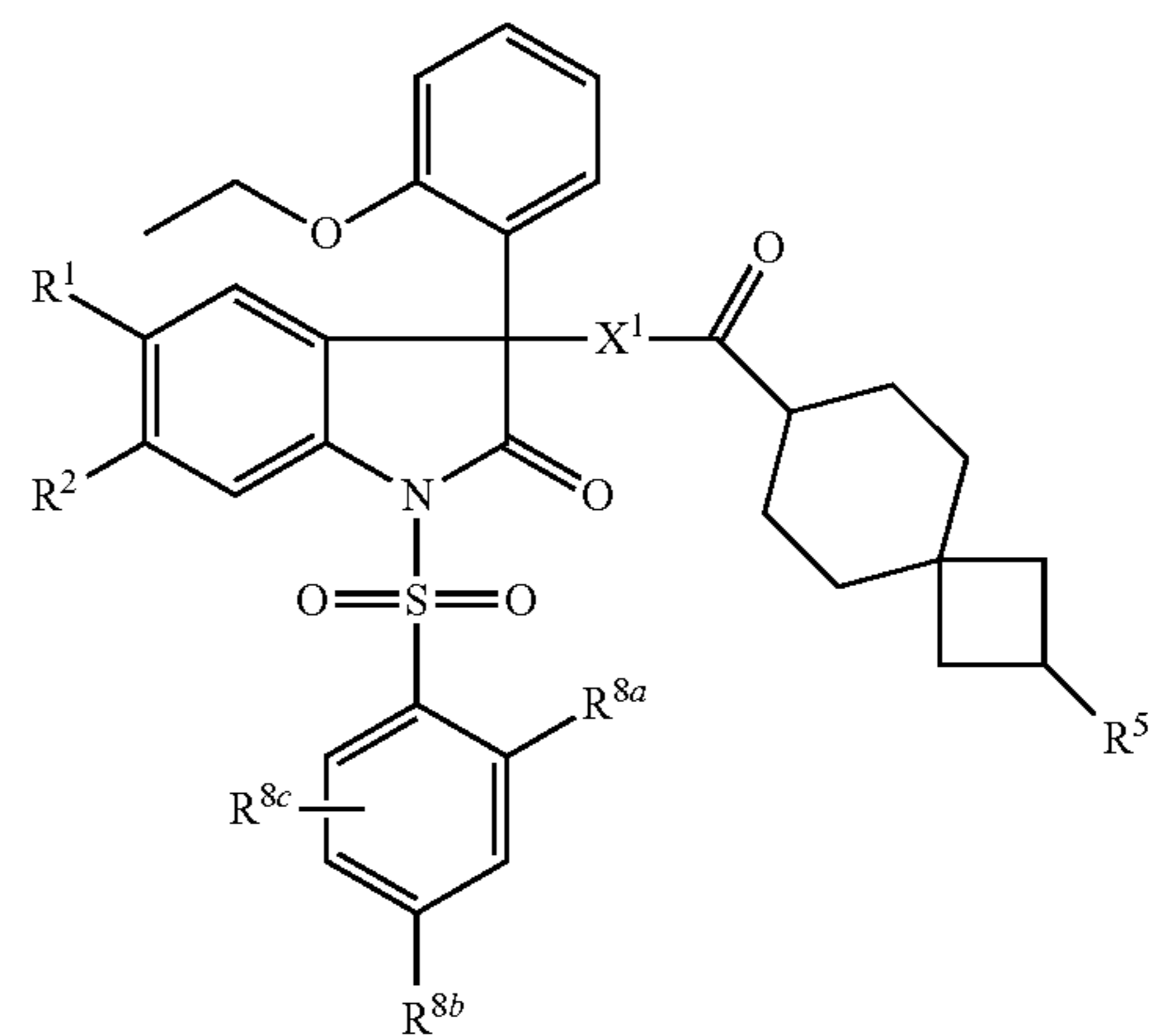
55

60

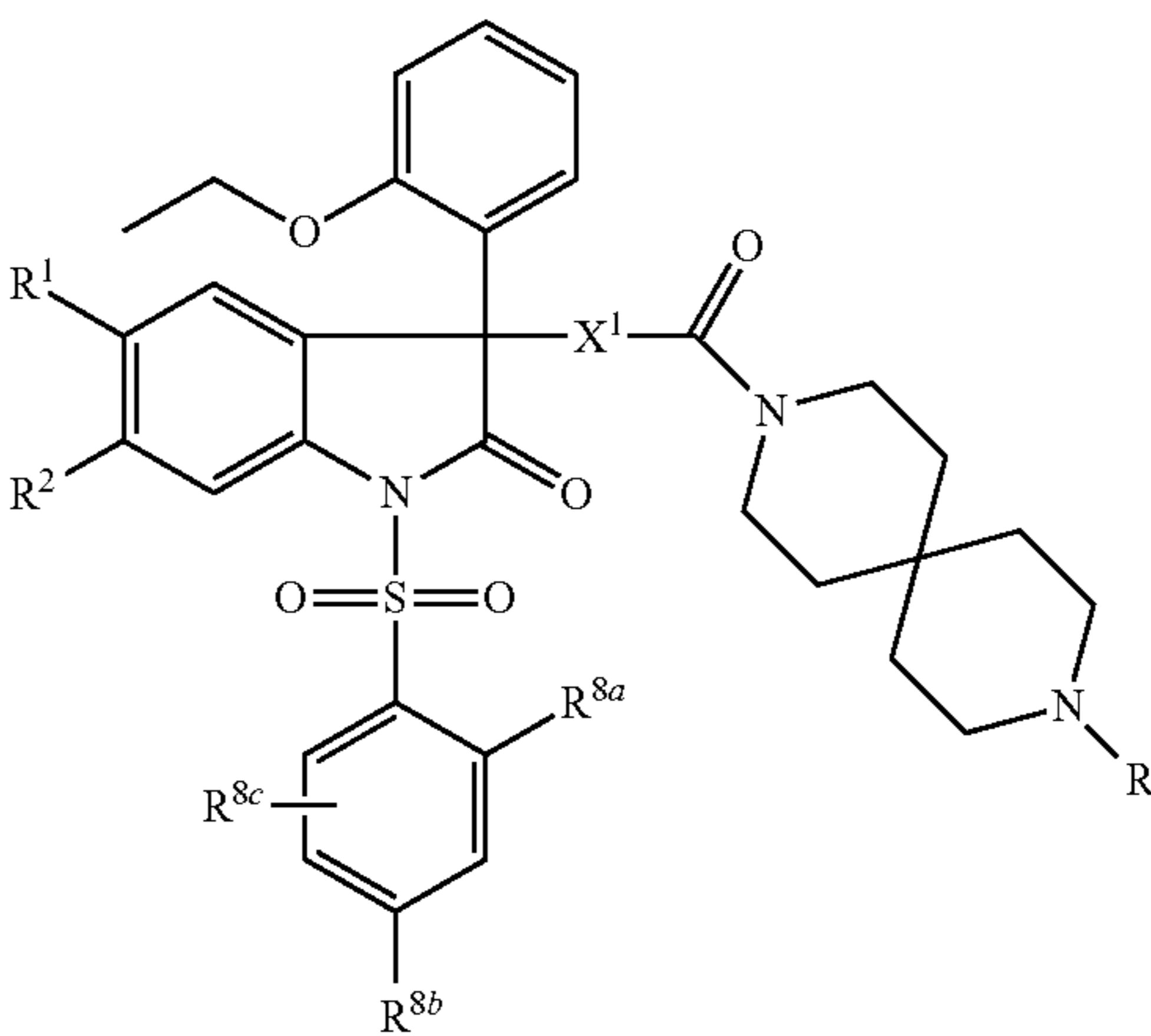
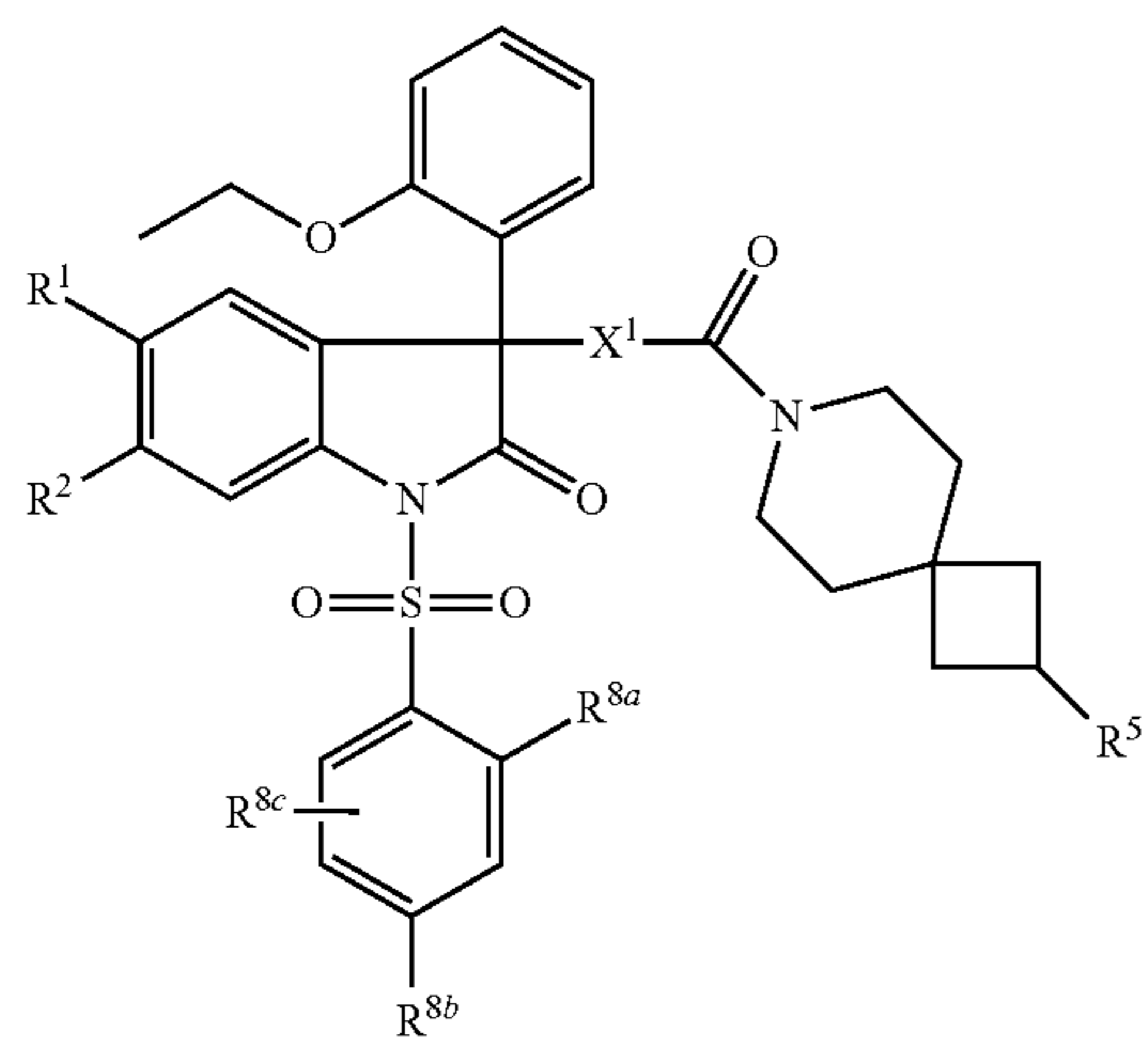
65

44

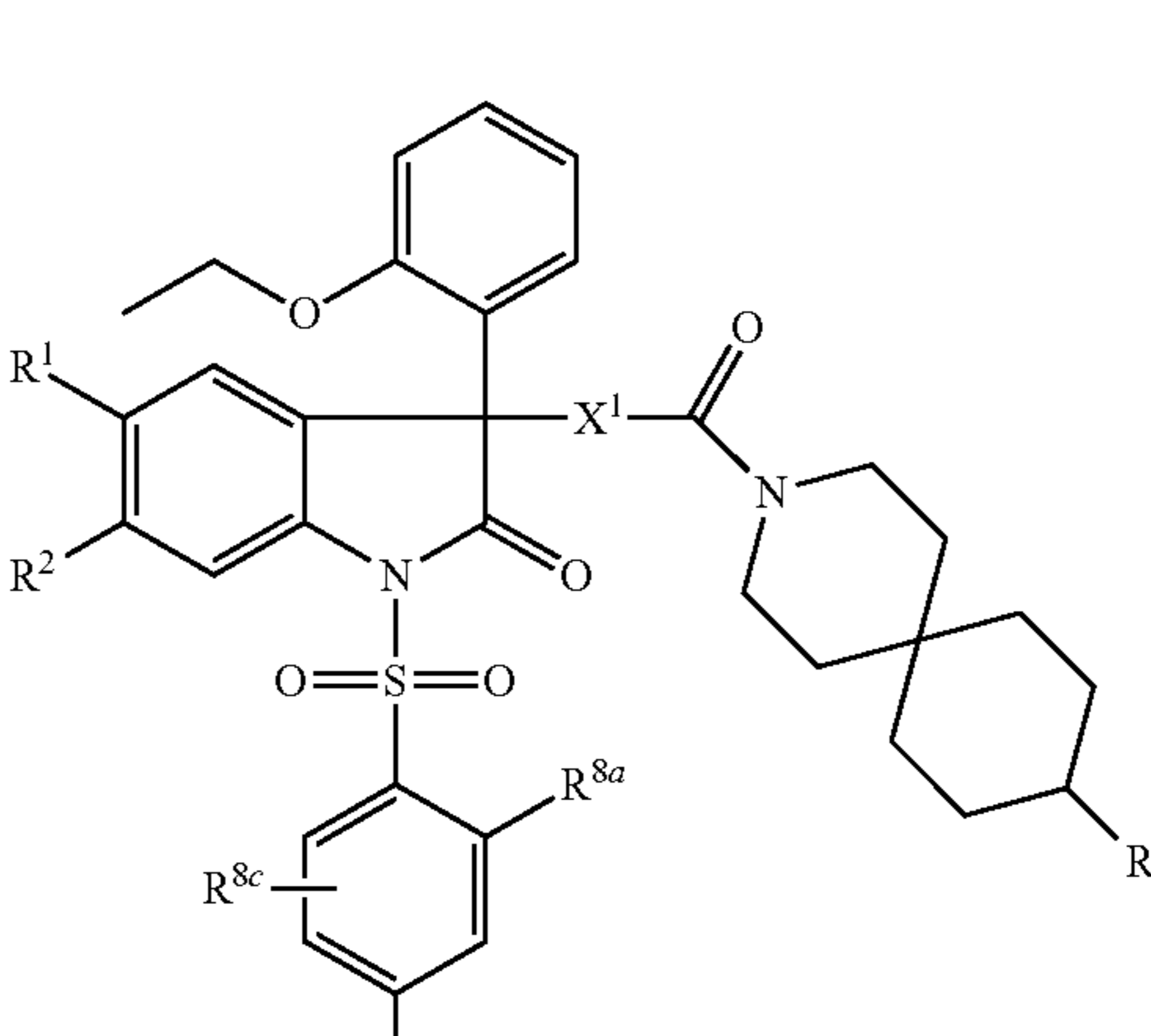
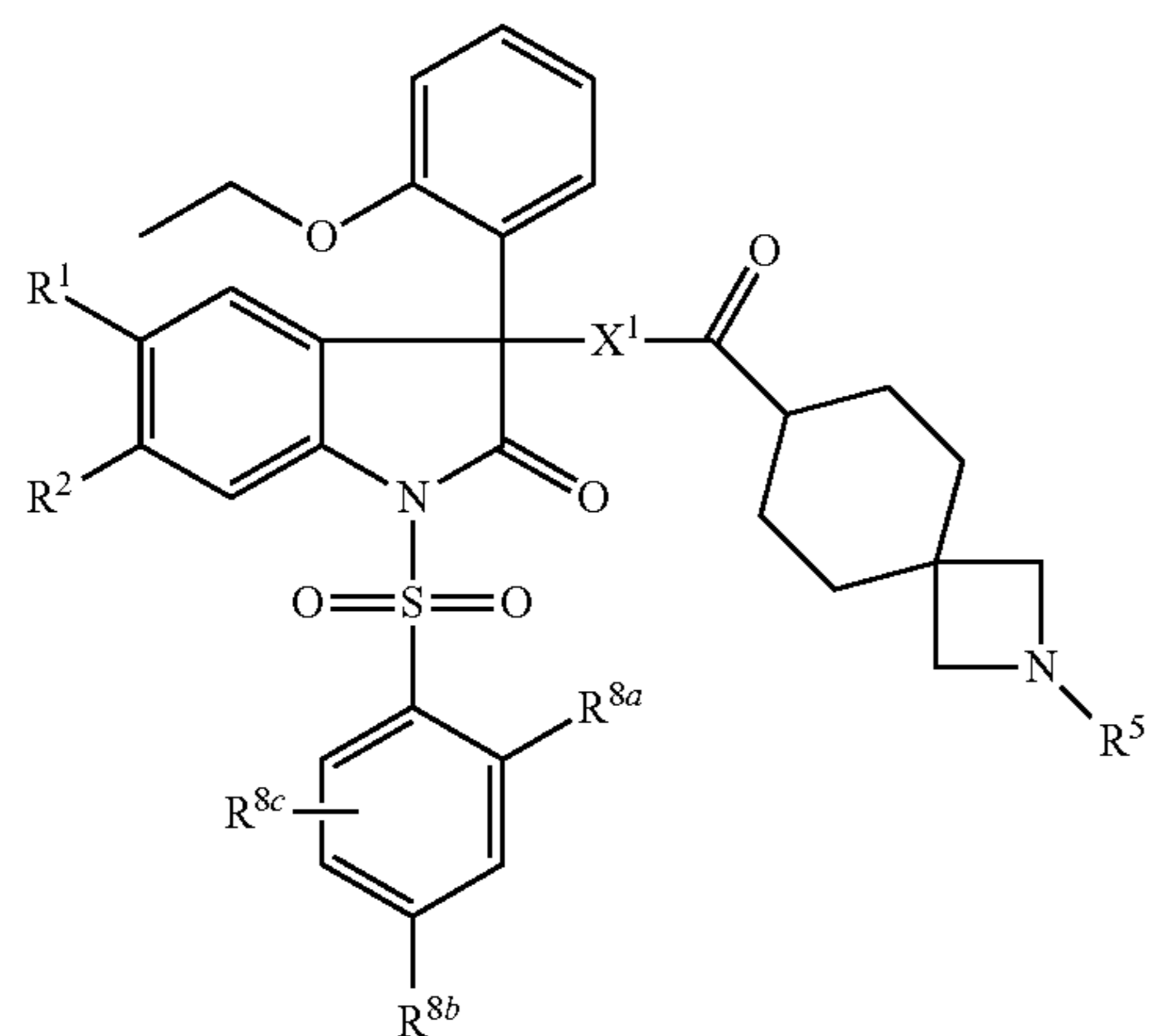
-continued



I.60



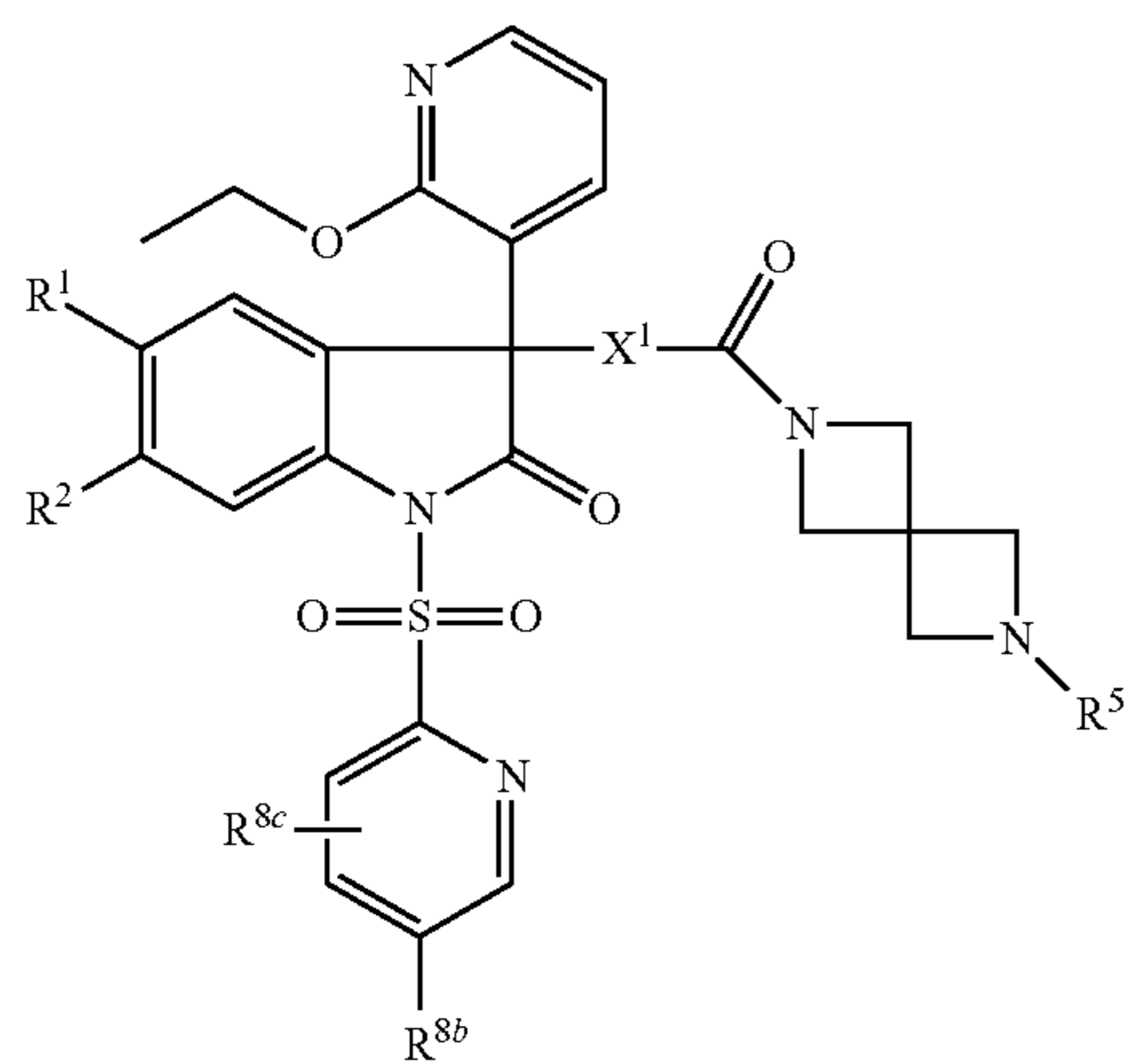
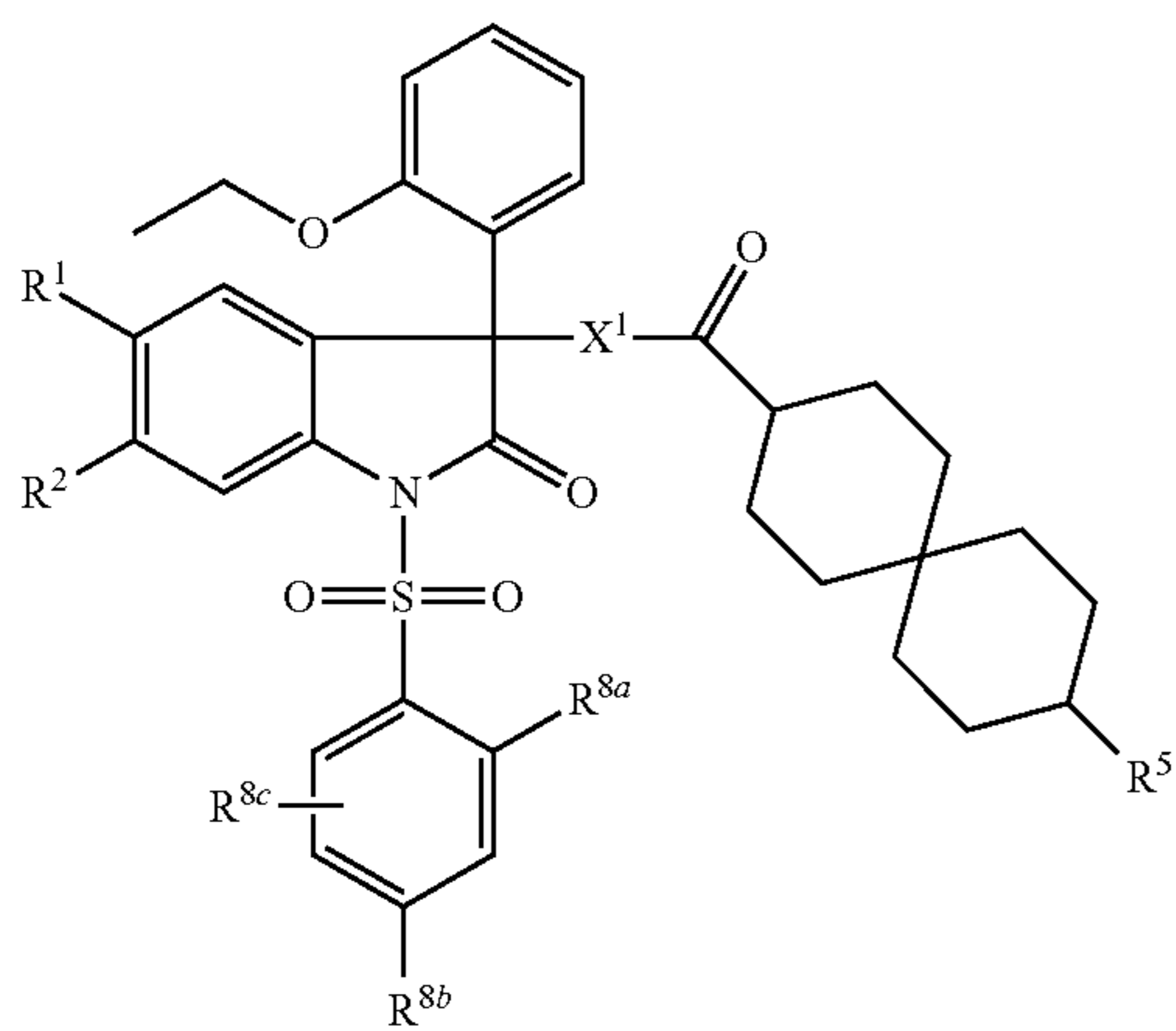
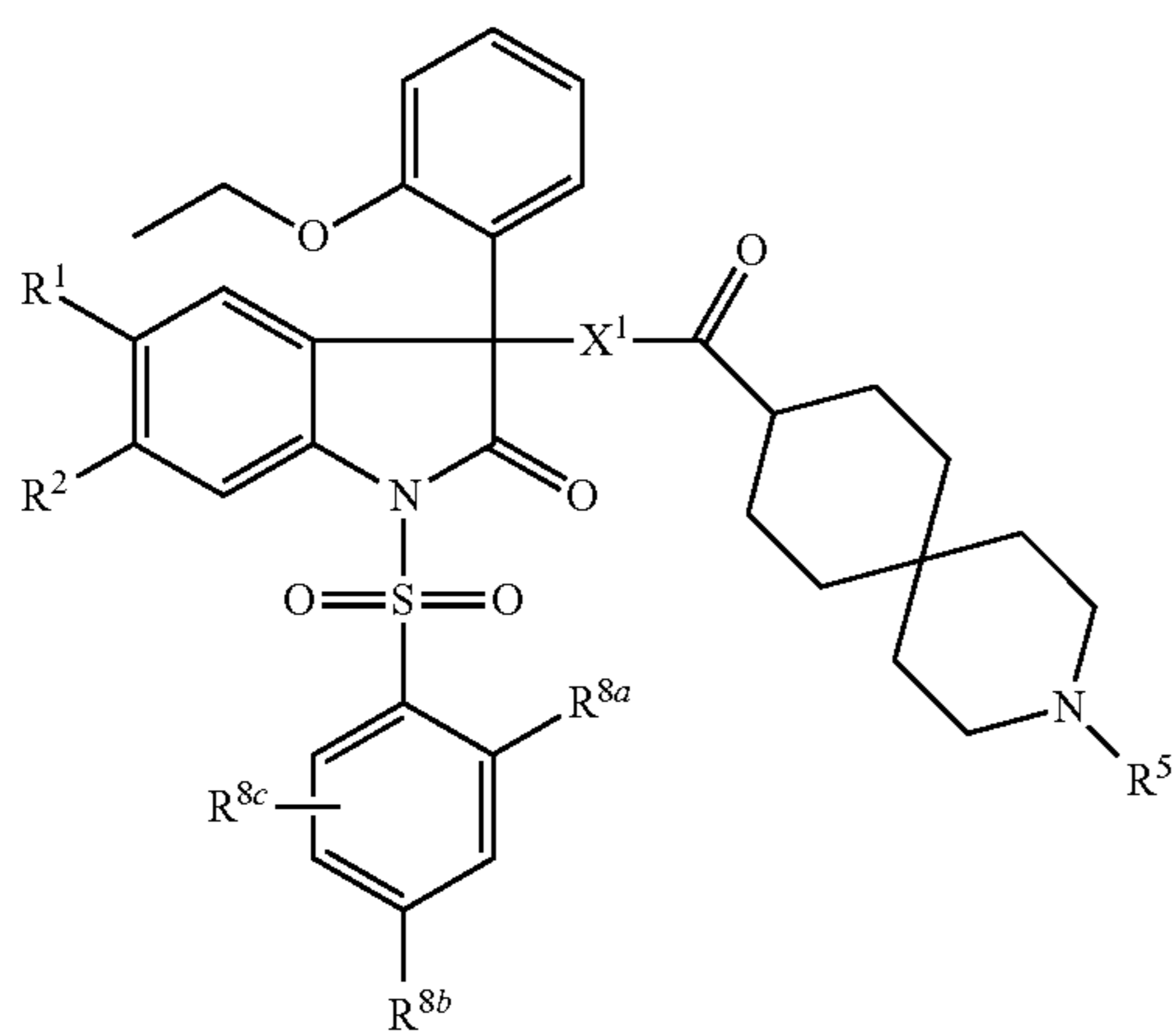
I.61



I.62

45

-continued



46

-continued

I.63

5

10

15

20

25

I.64

30

35

40

45

I.65

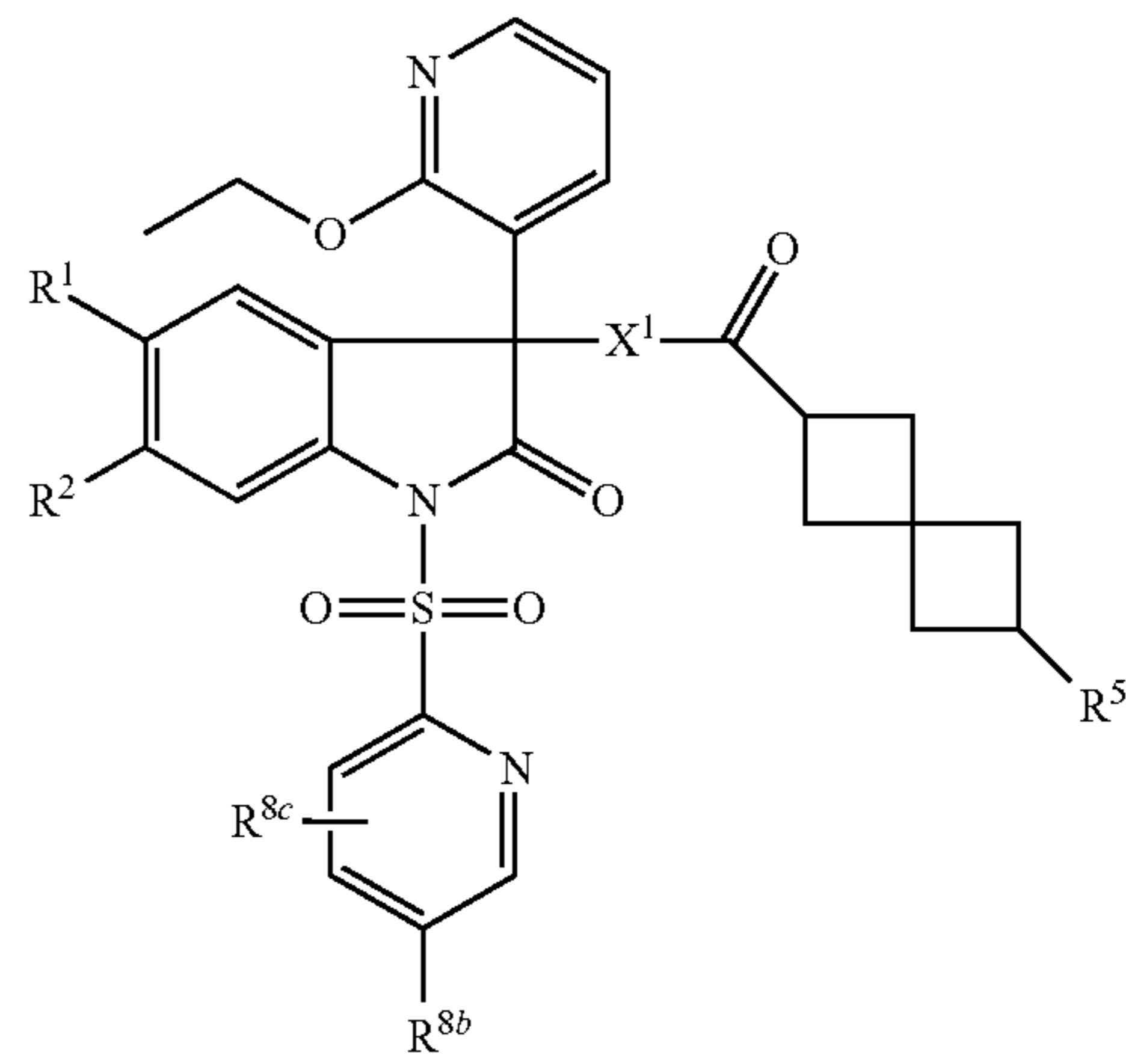
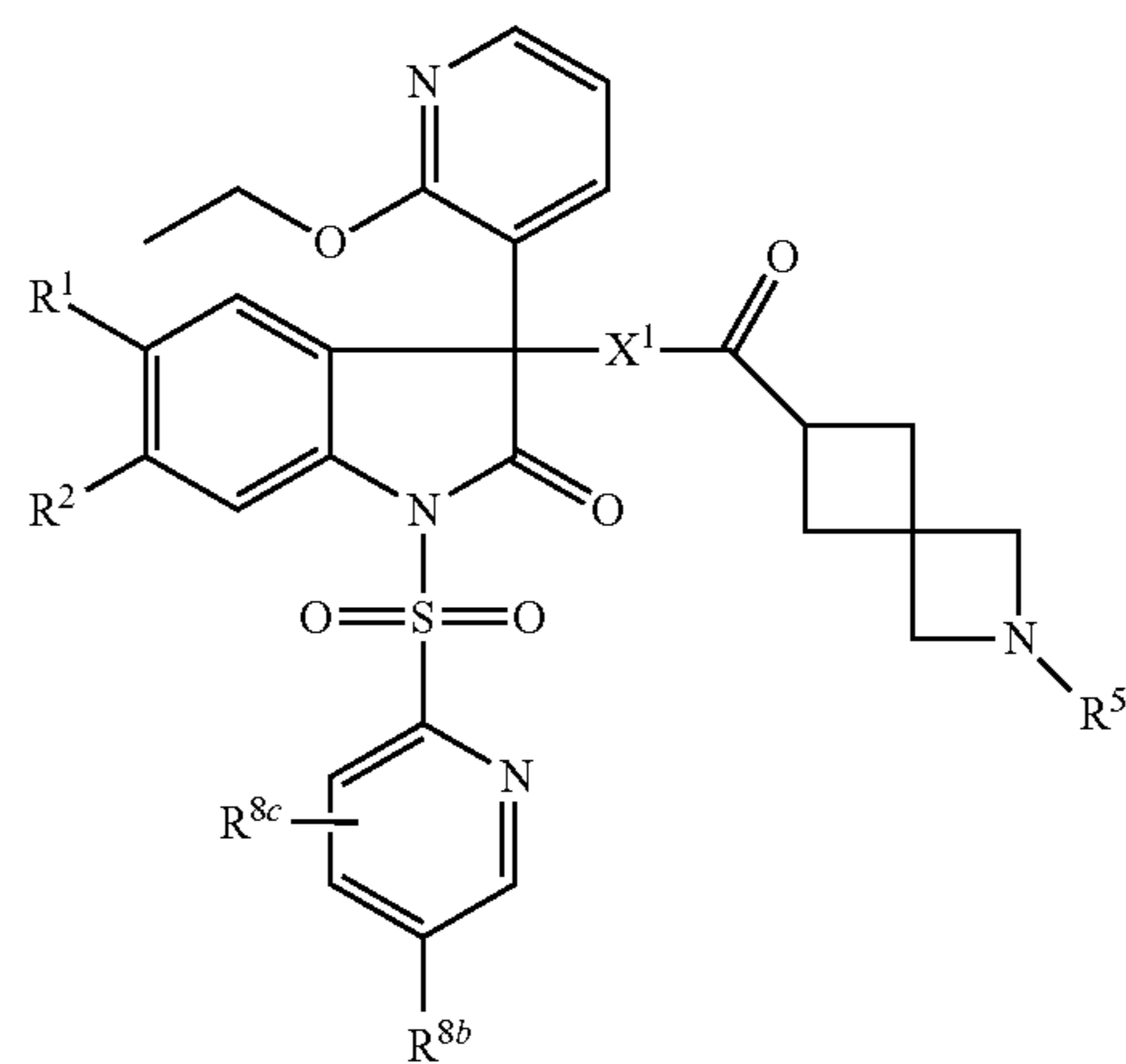
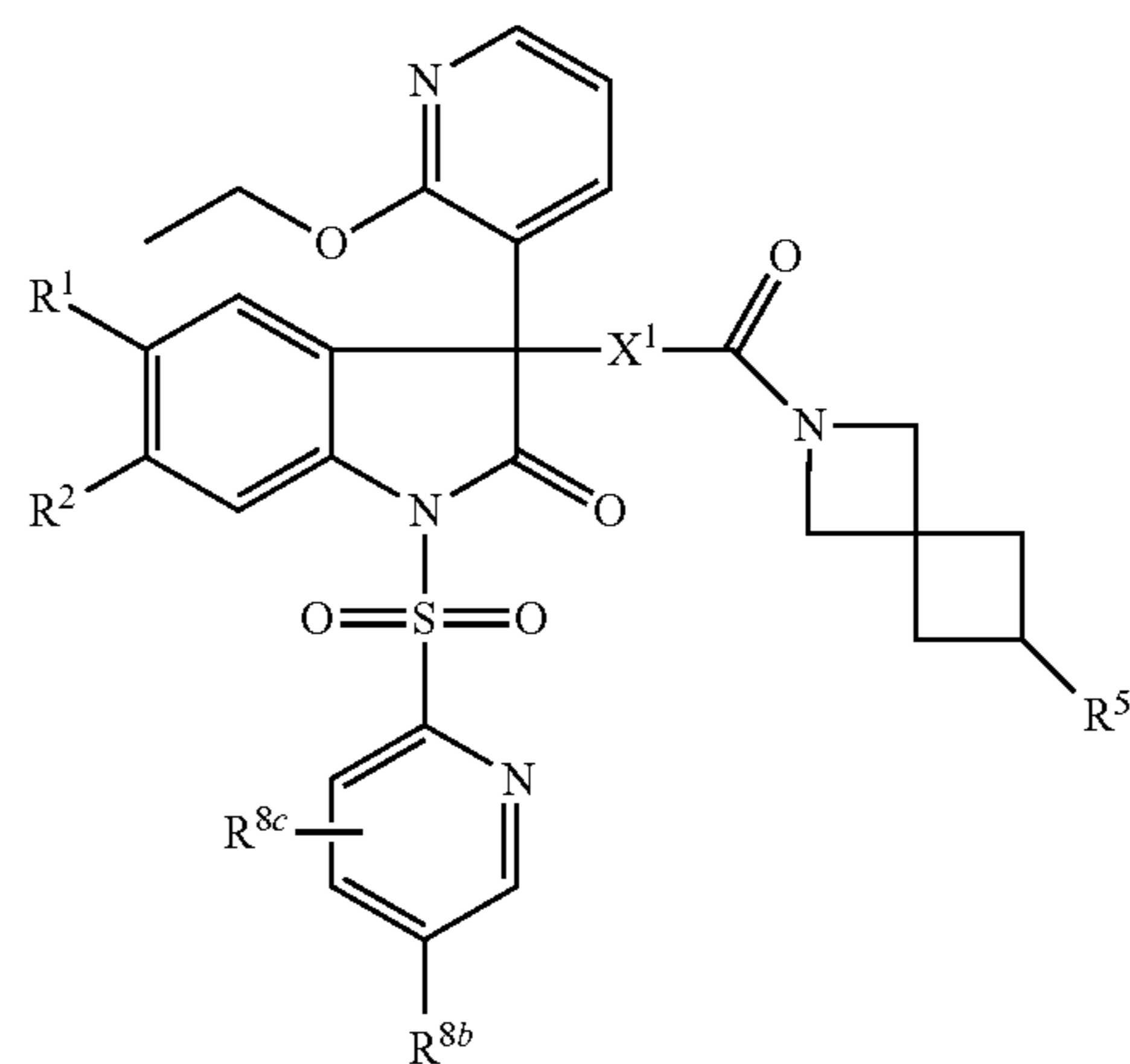
50

55

60

65

I.66

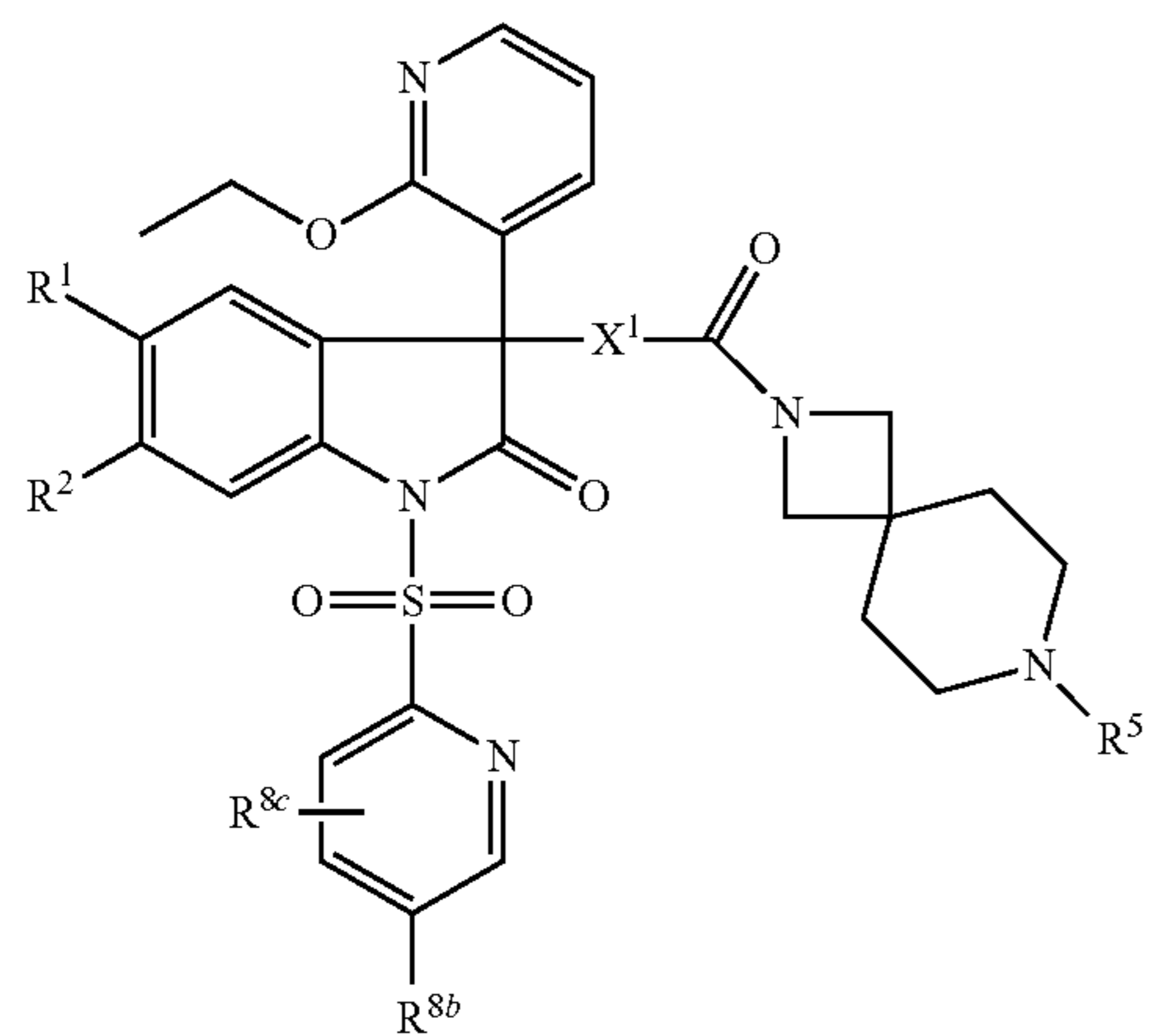


I.67

I.68

47

-continued



I.69

5

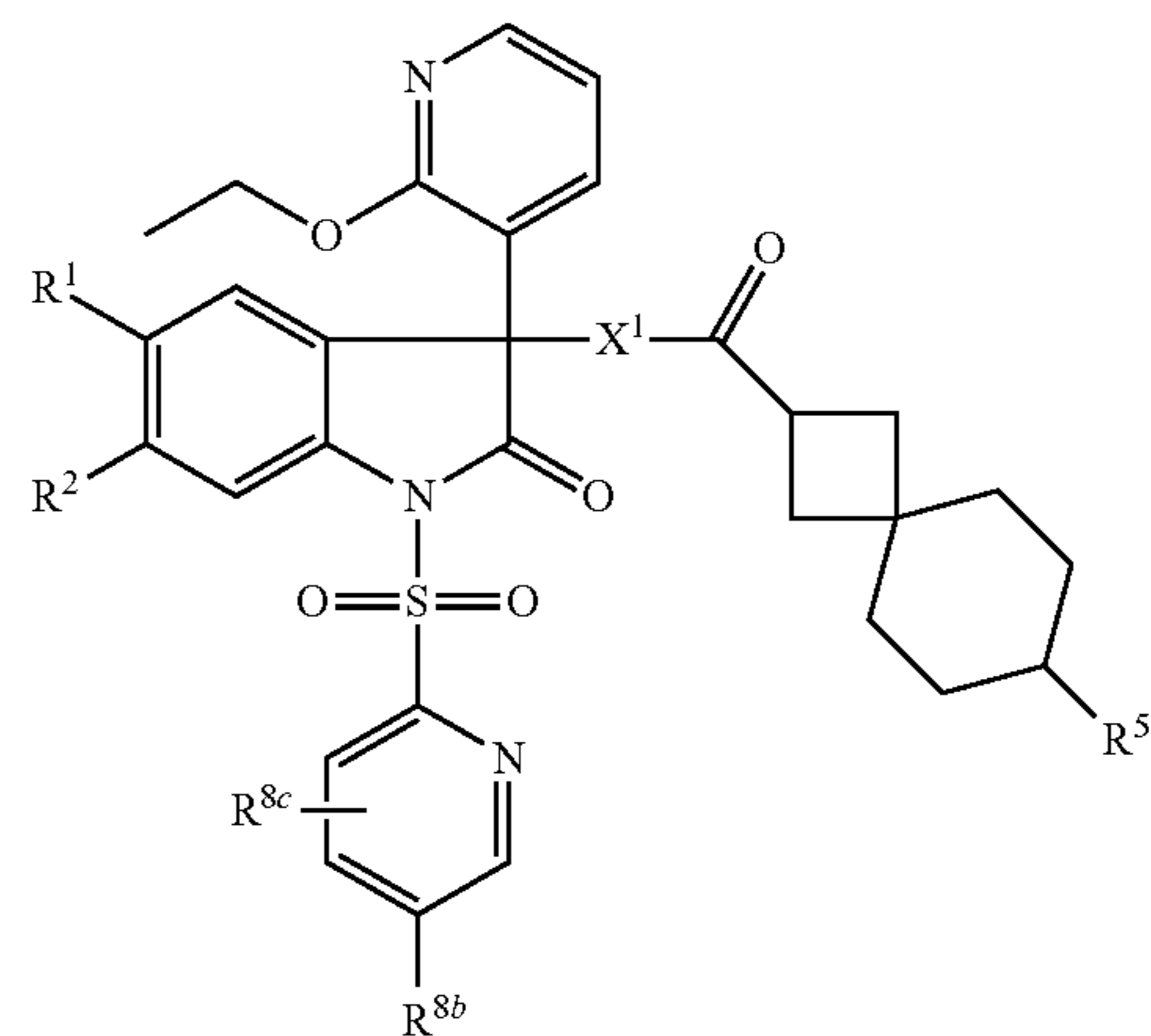
10

15

20

48

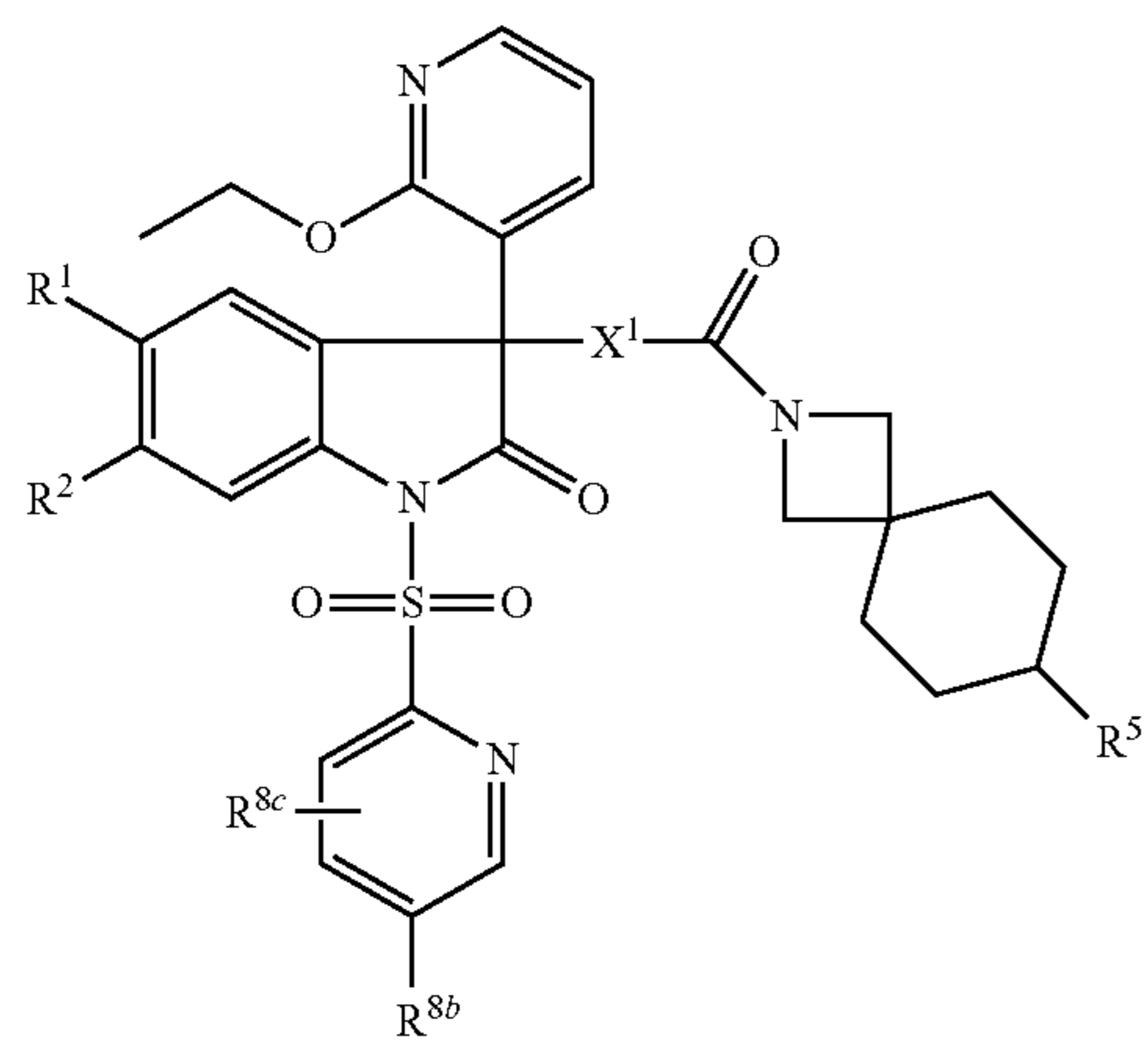
-continued



I.72

I.70

25

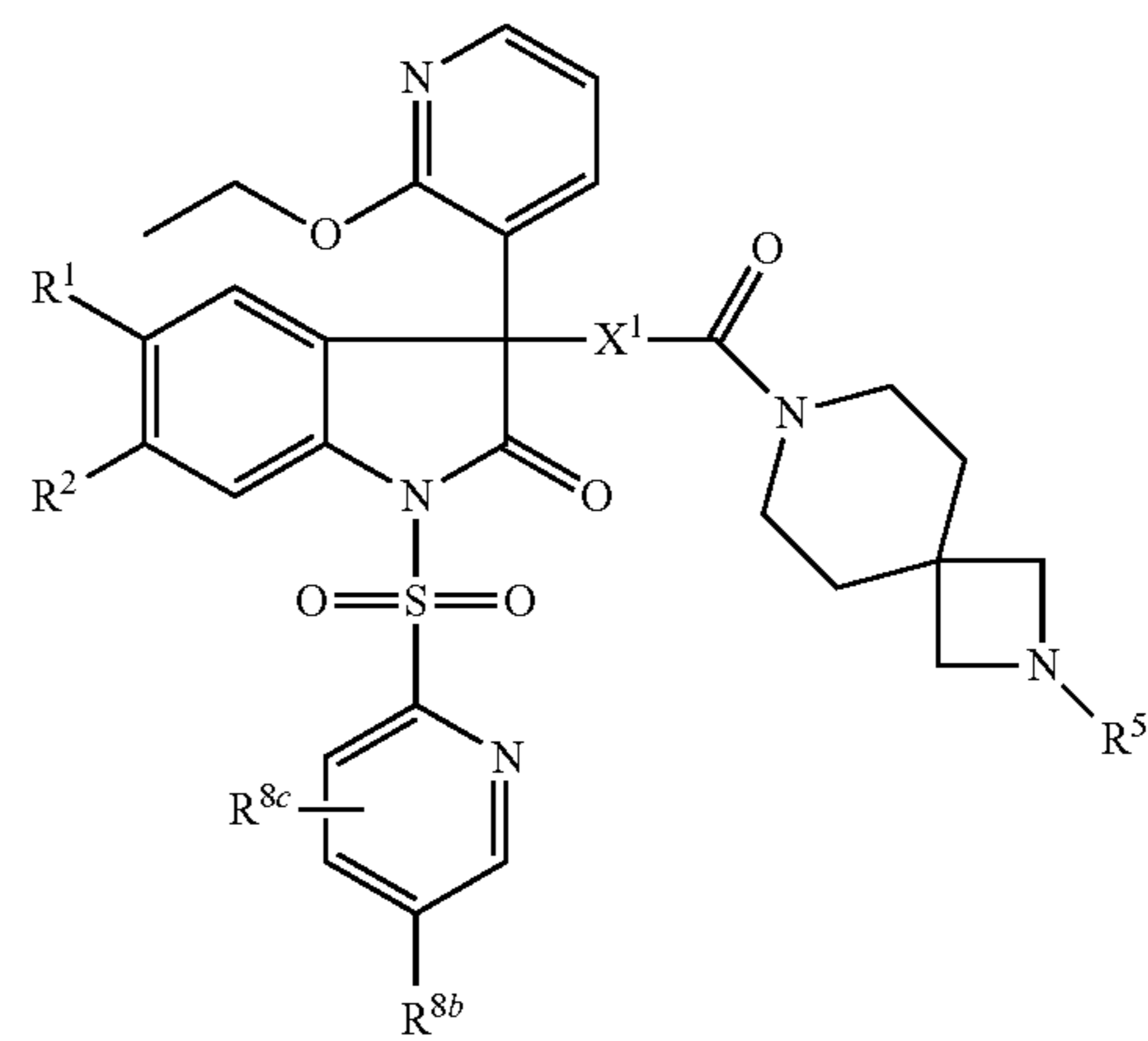


30

35

40

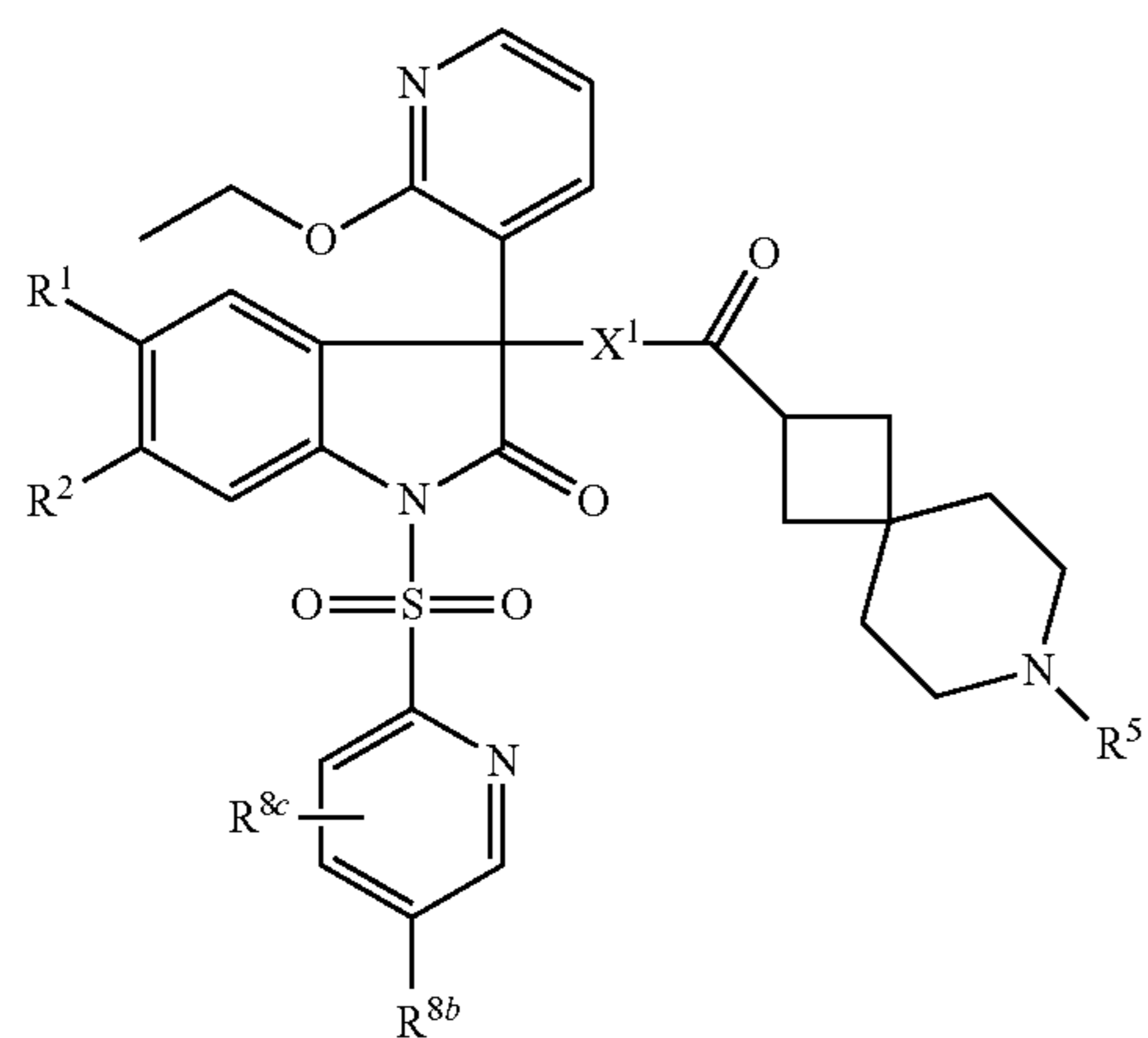
45



I.73

I.71

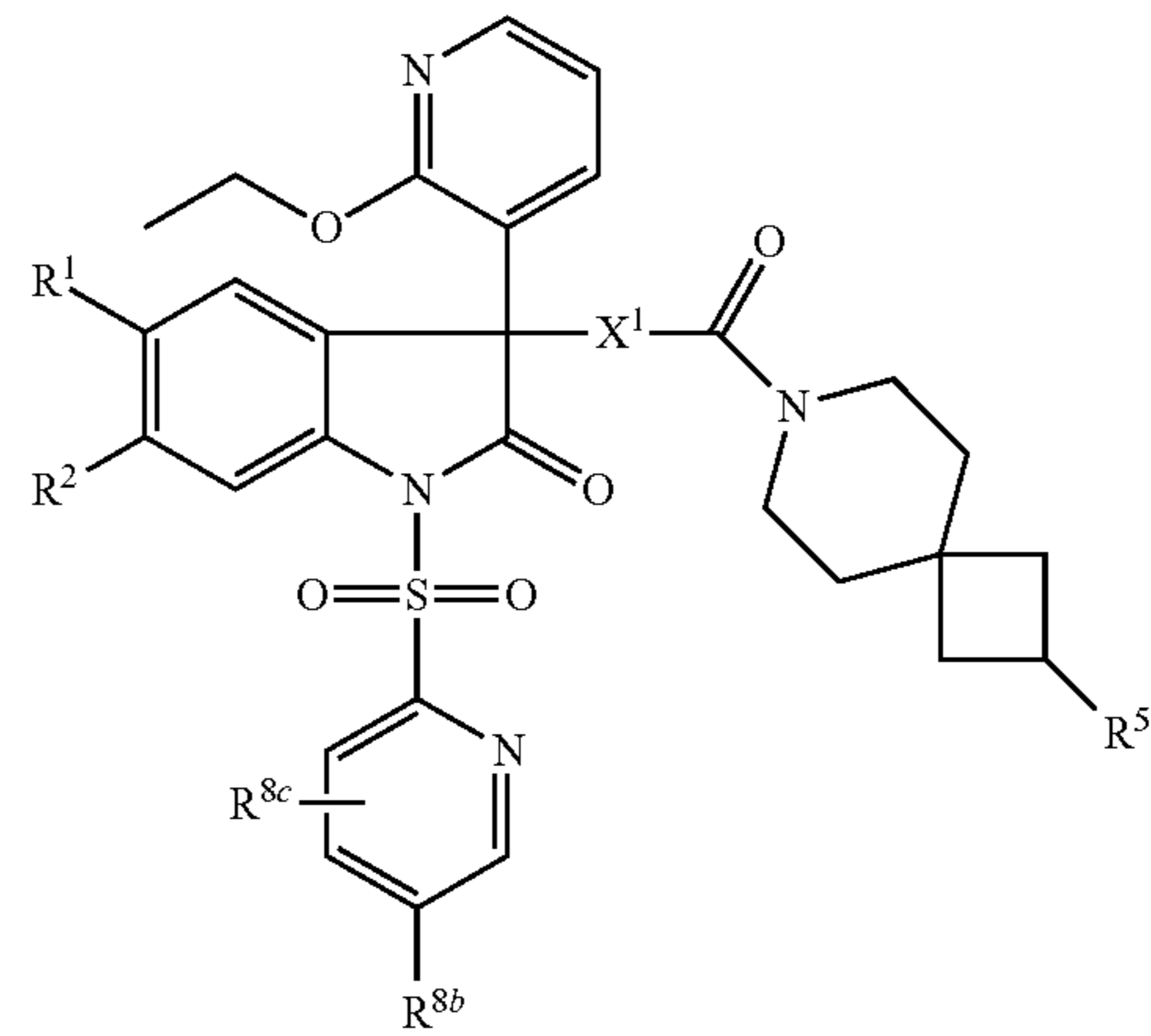
50



55

60

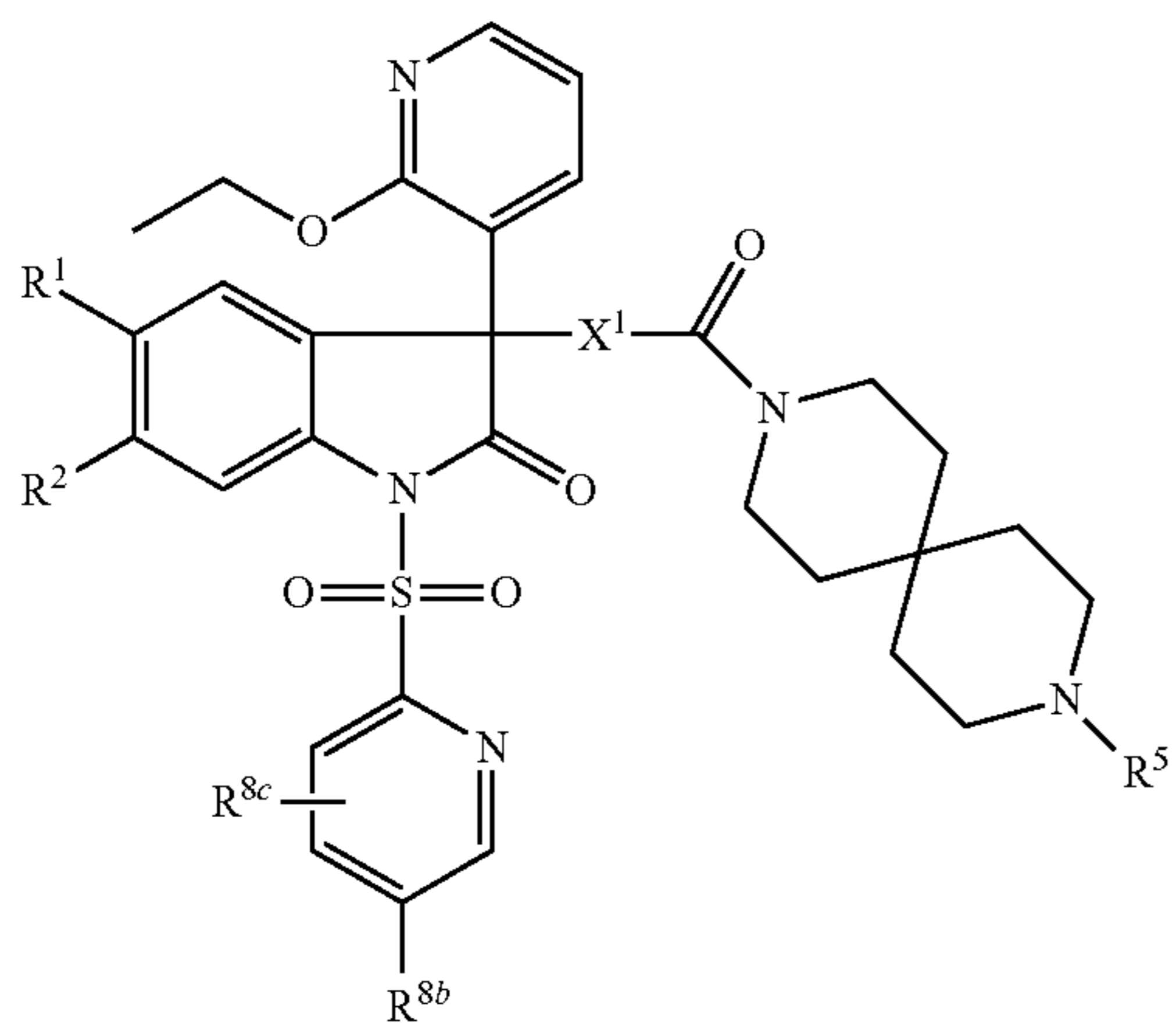
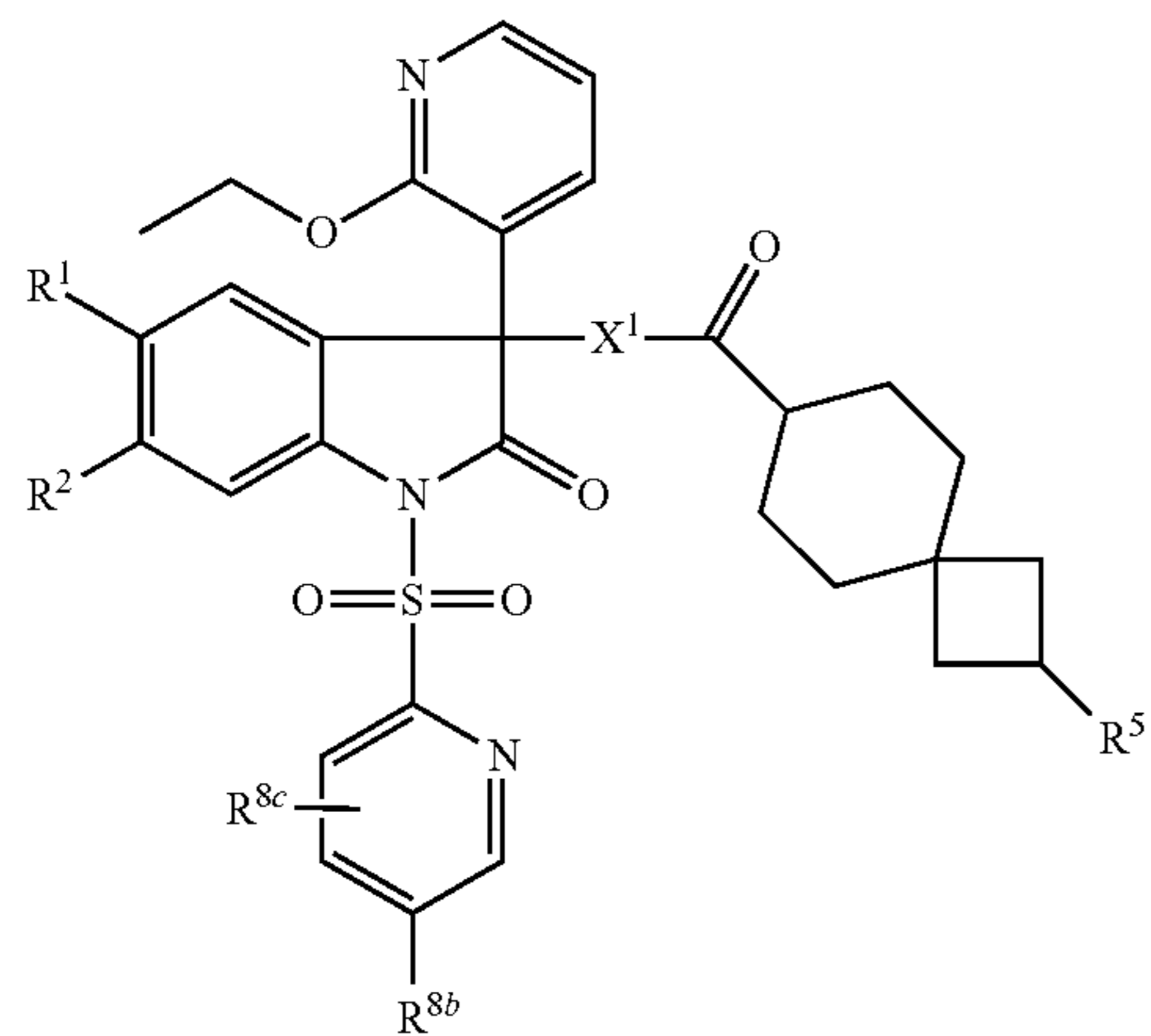
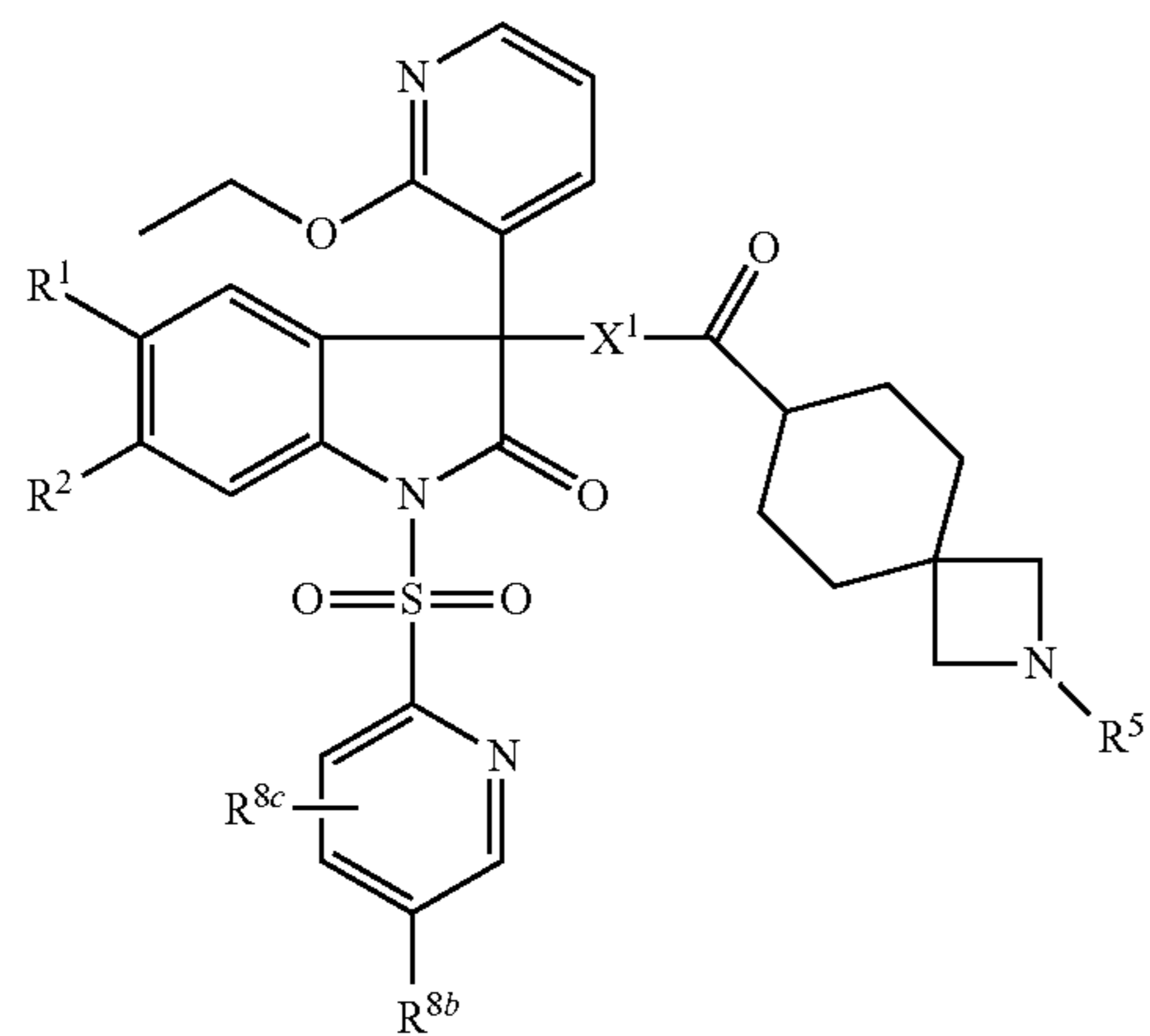
65



I.74

49

-continued



50

-continued

I.75

5

10

15

20

25

I.76

30

35

40

45

I.77

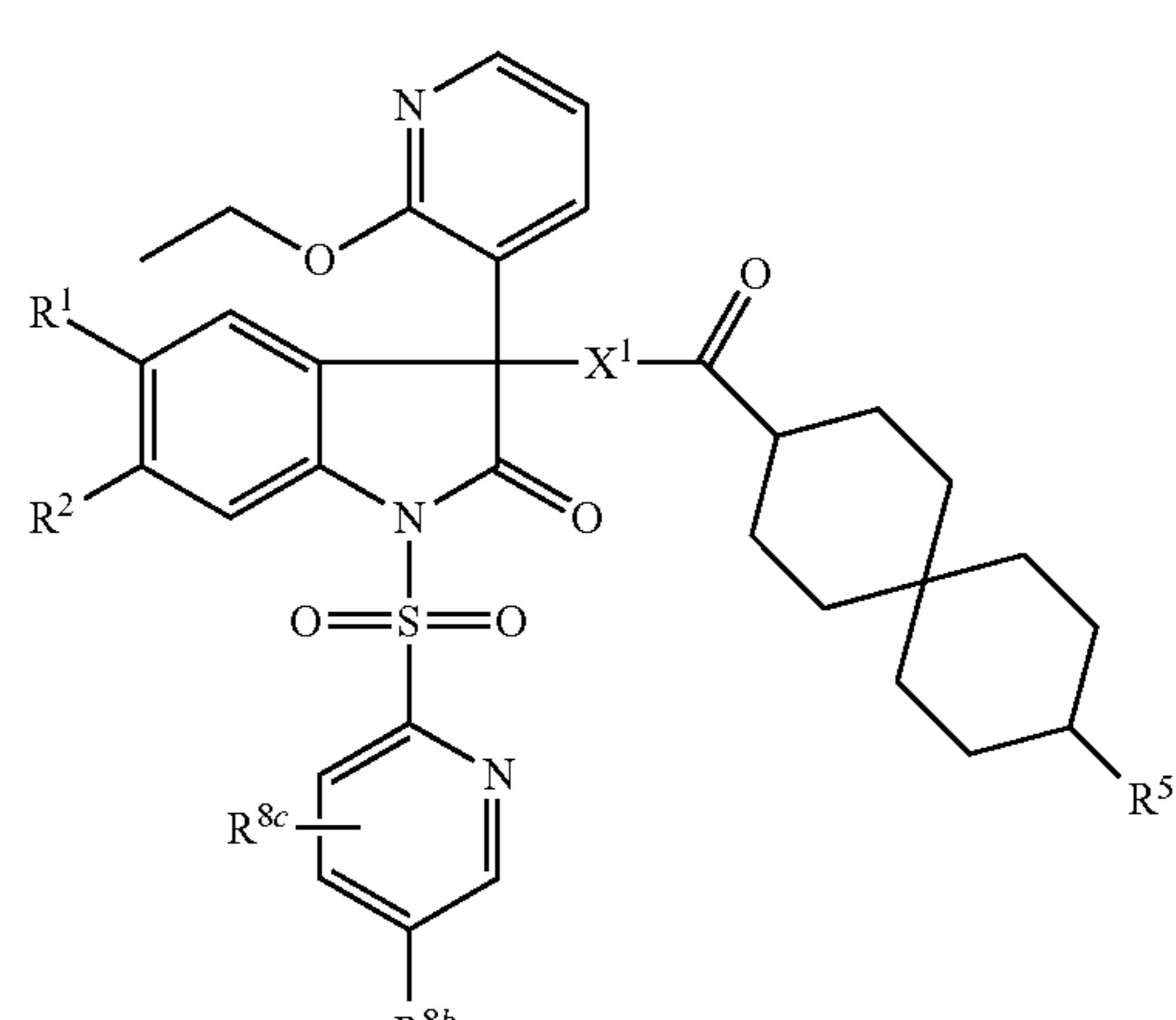
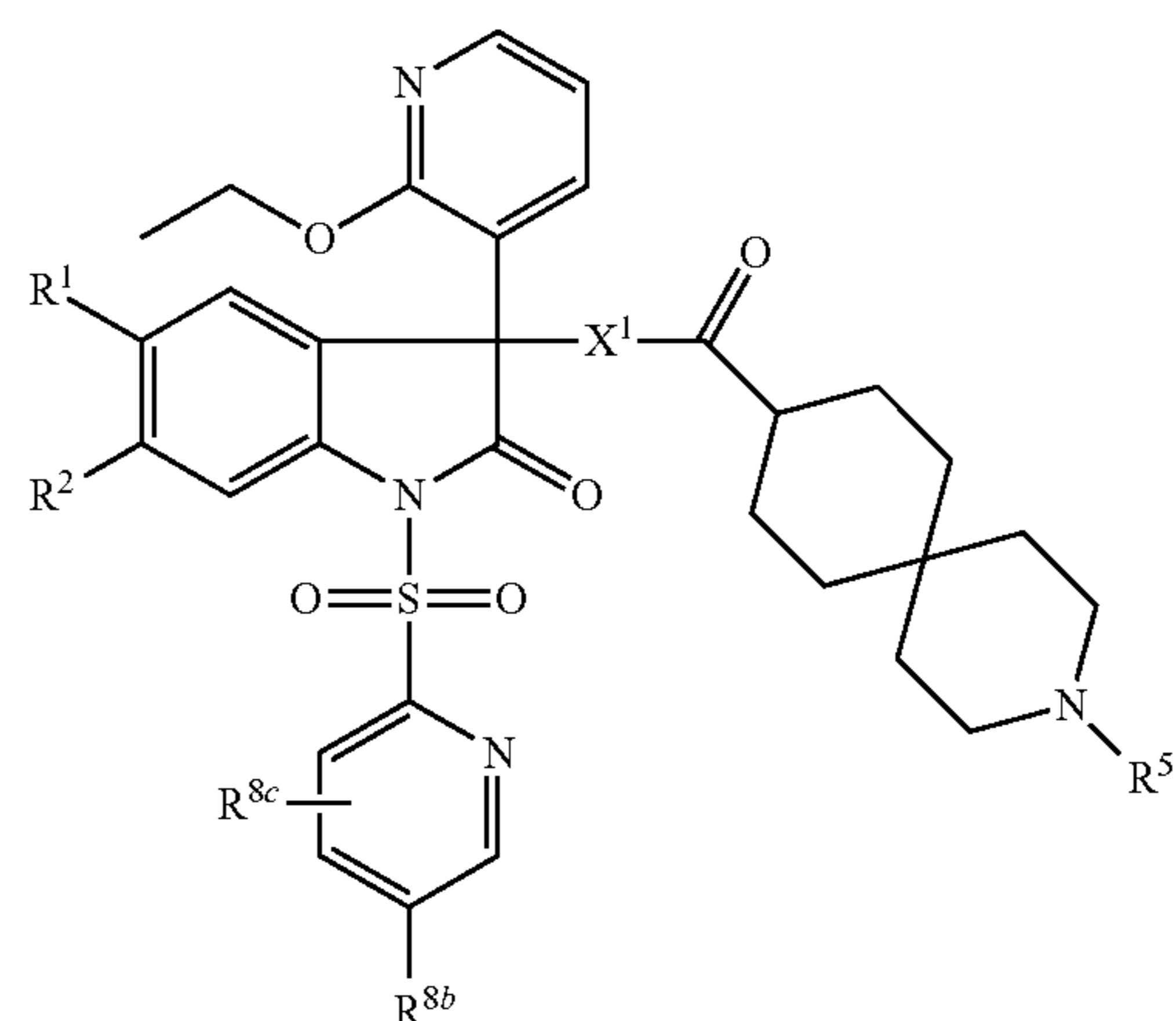
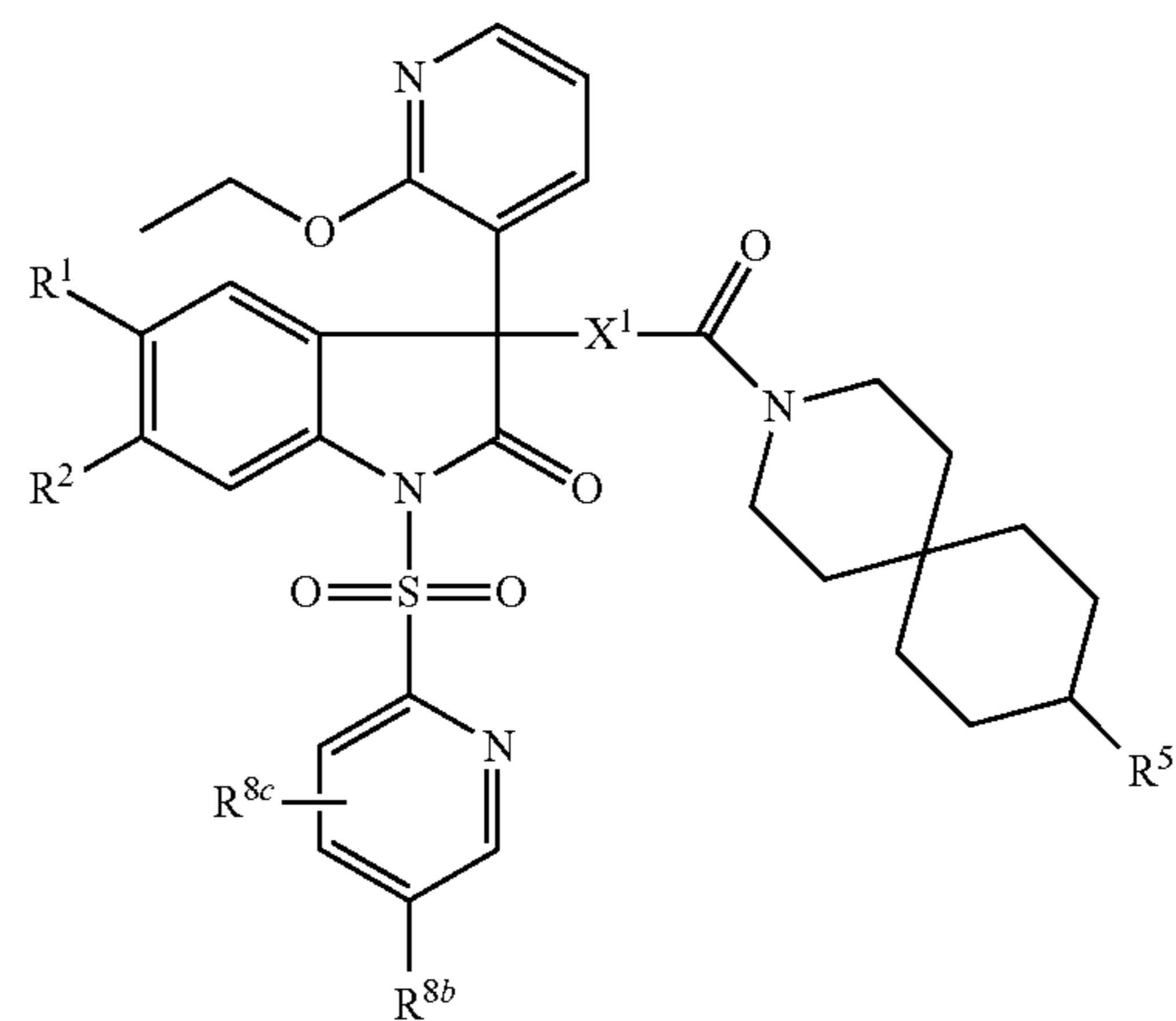
50

55

60

65

I.78

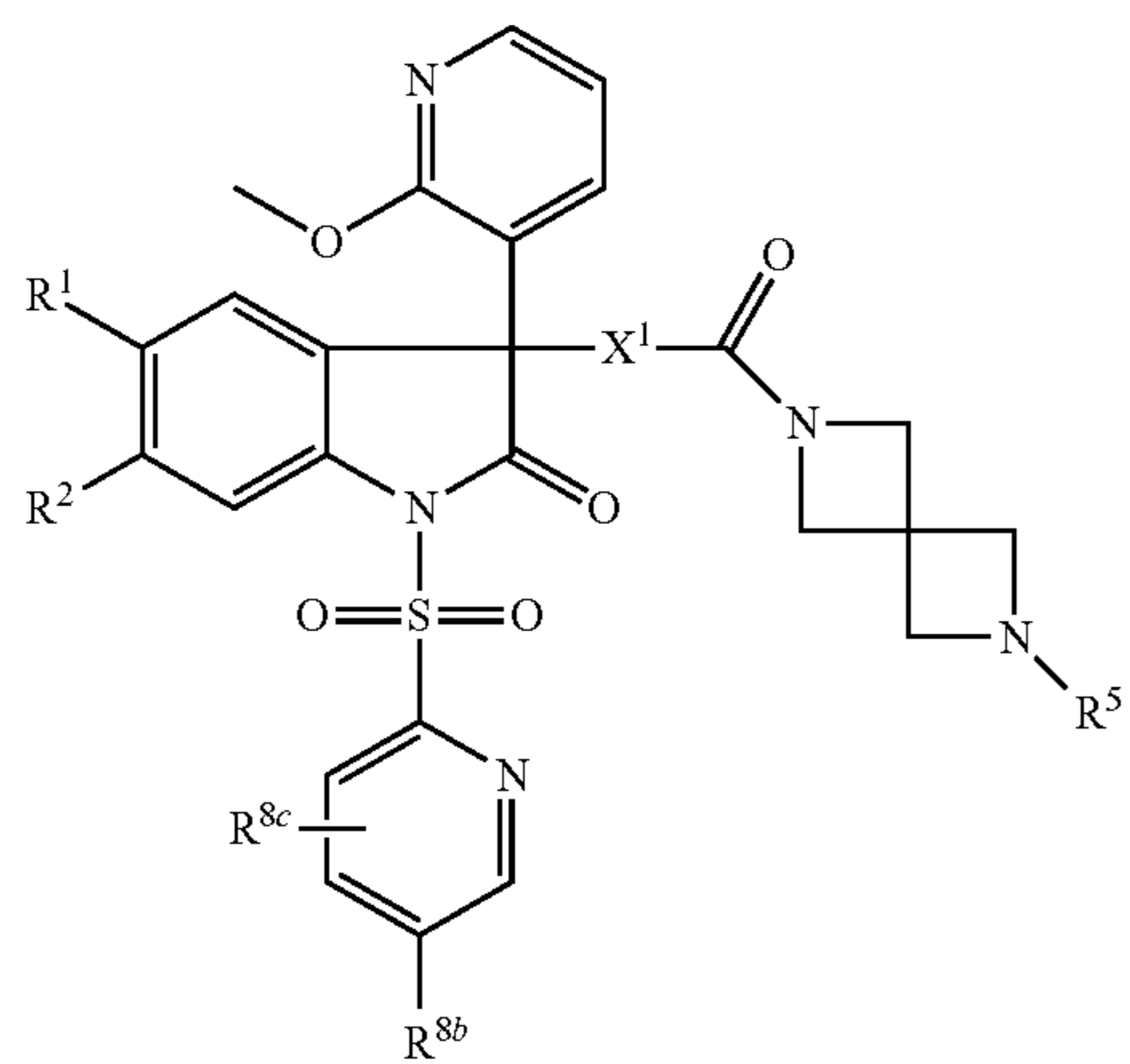


I.79

I.80

51

-continued



I.81

5

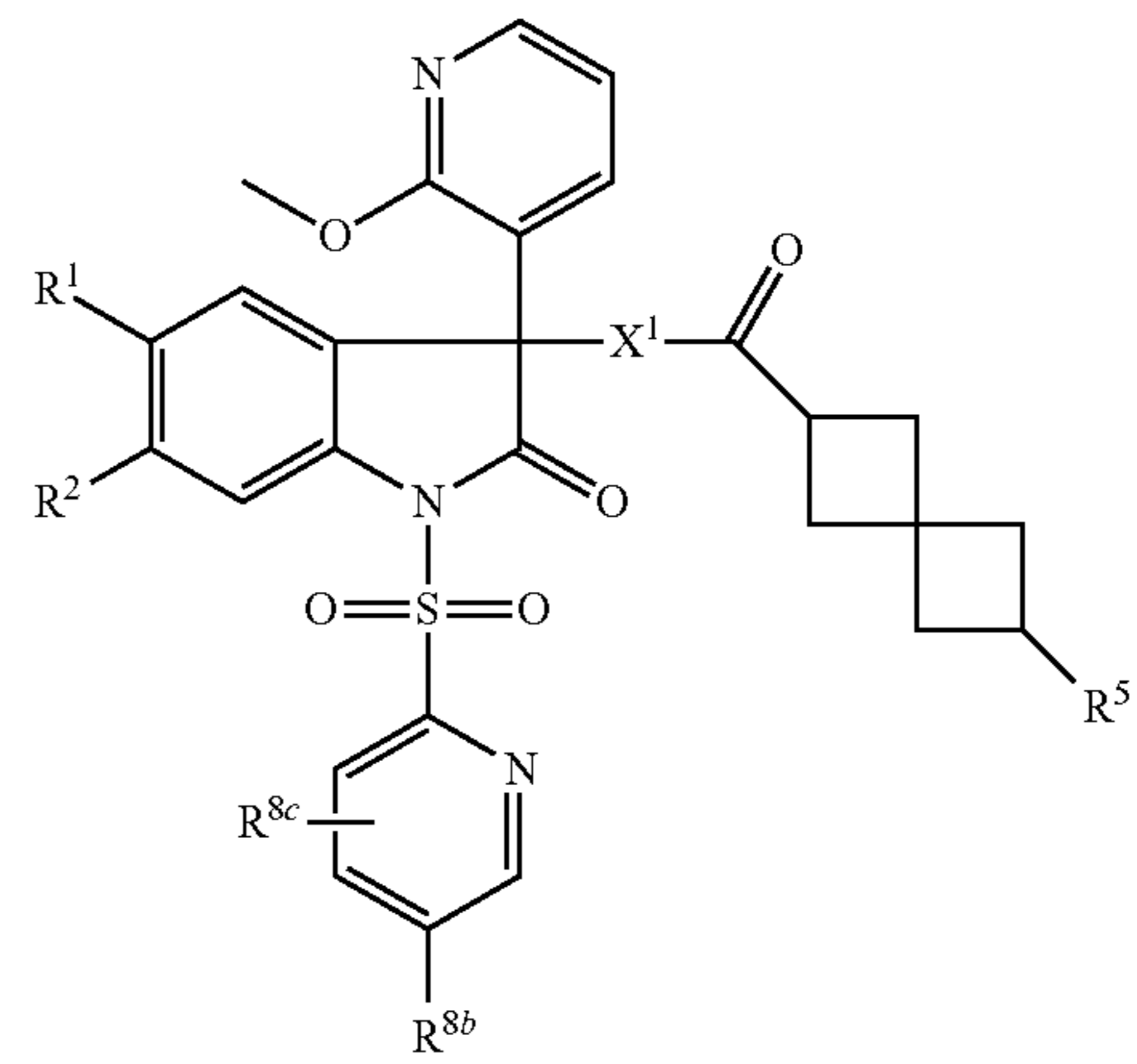
10

15

20

52

-continued



I.84

I.82

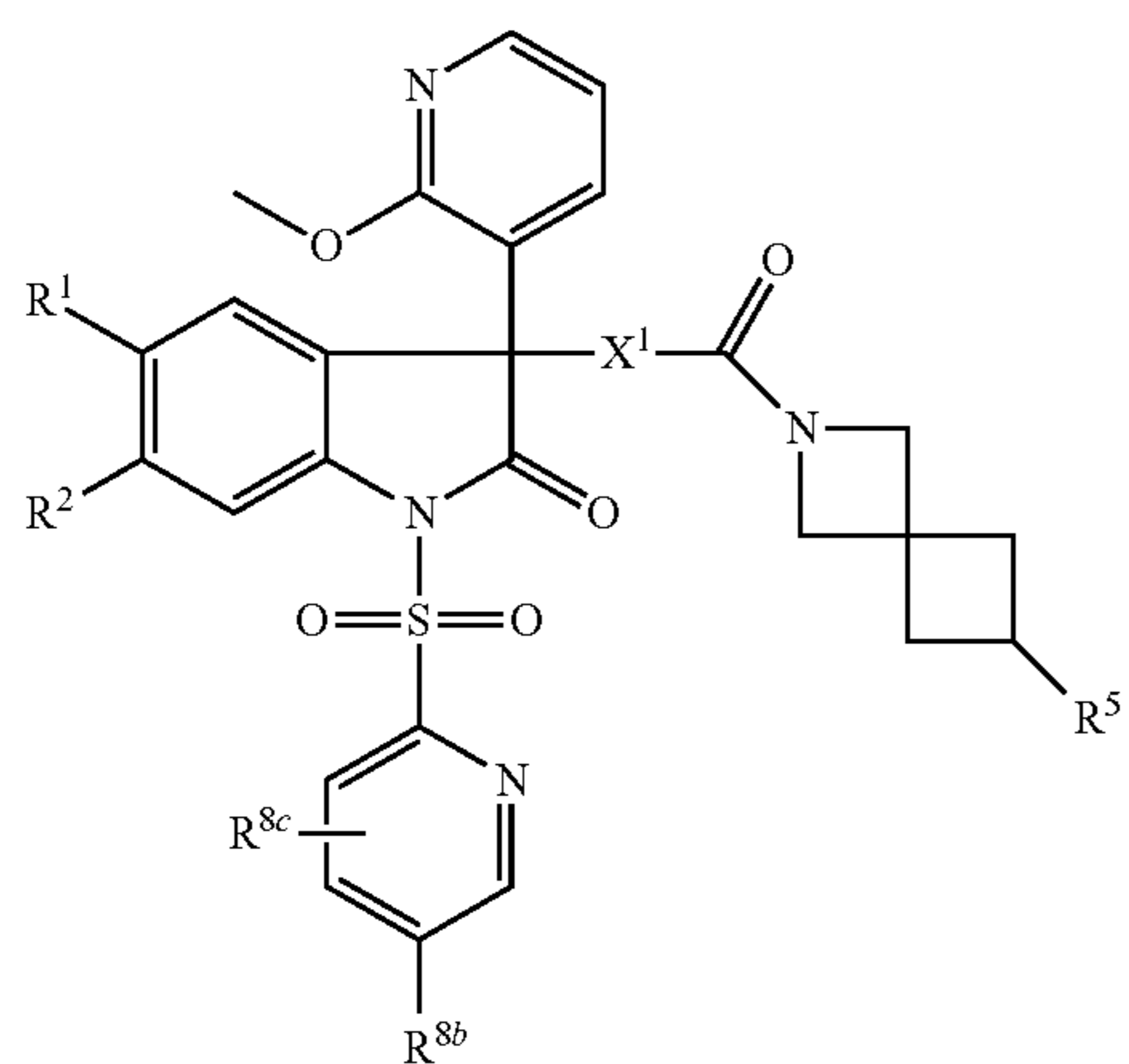
25

30

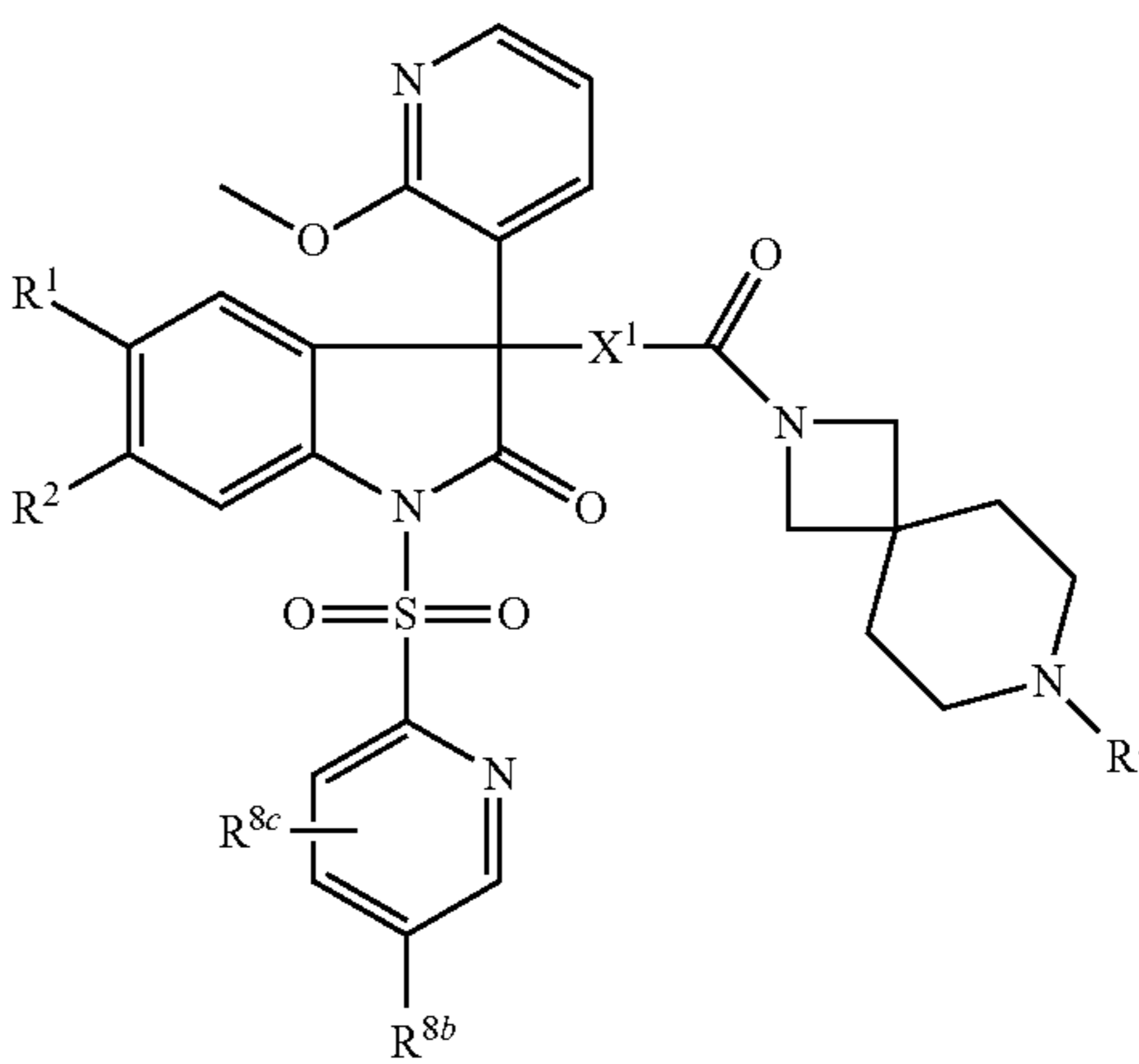
35

40

45



I.85



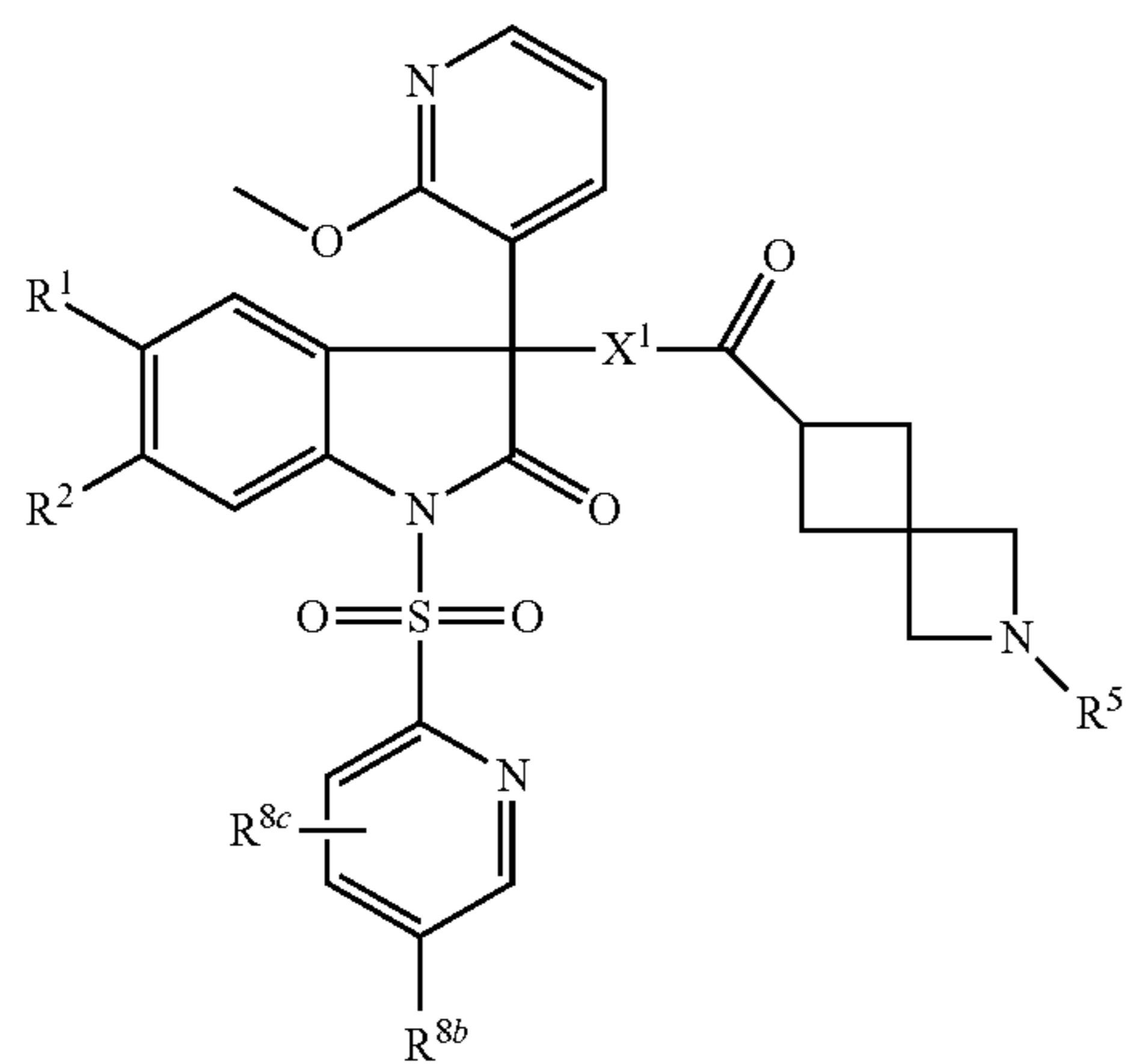
I.83

50

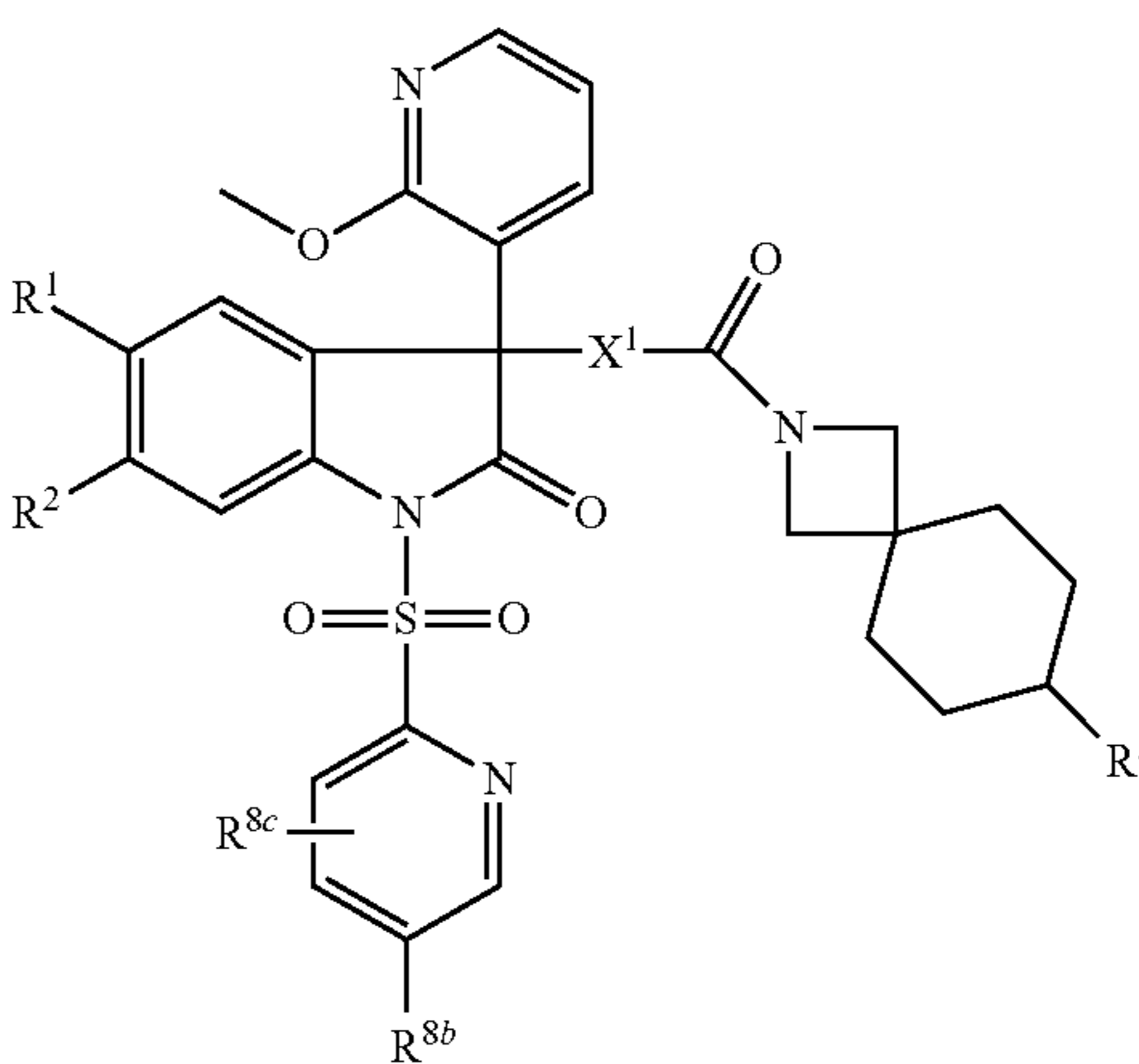
55

60

65

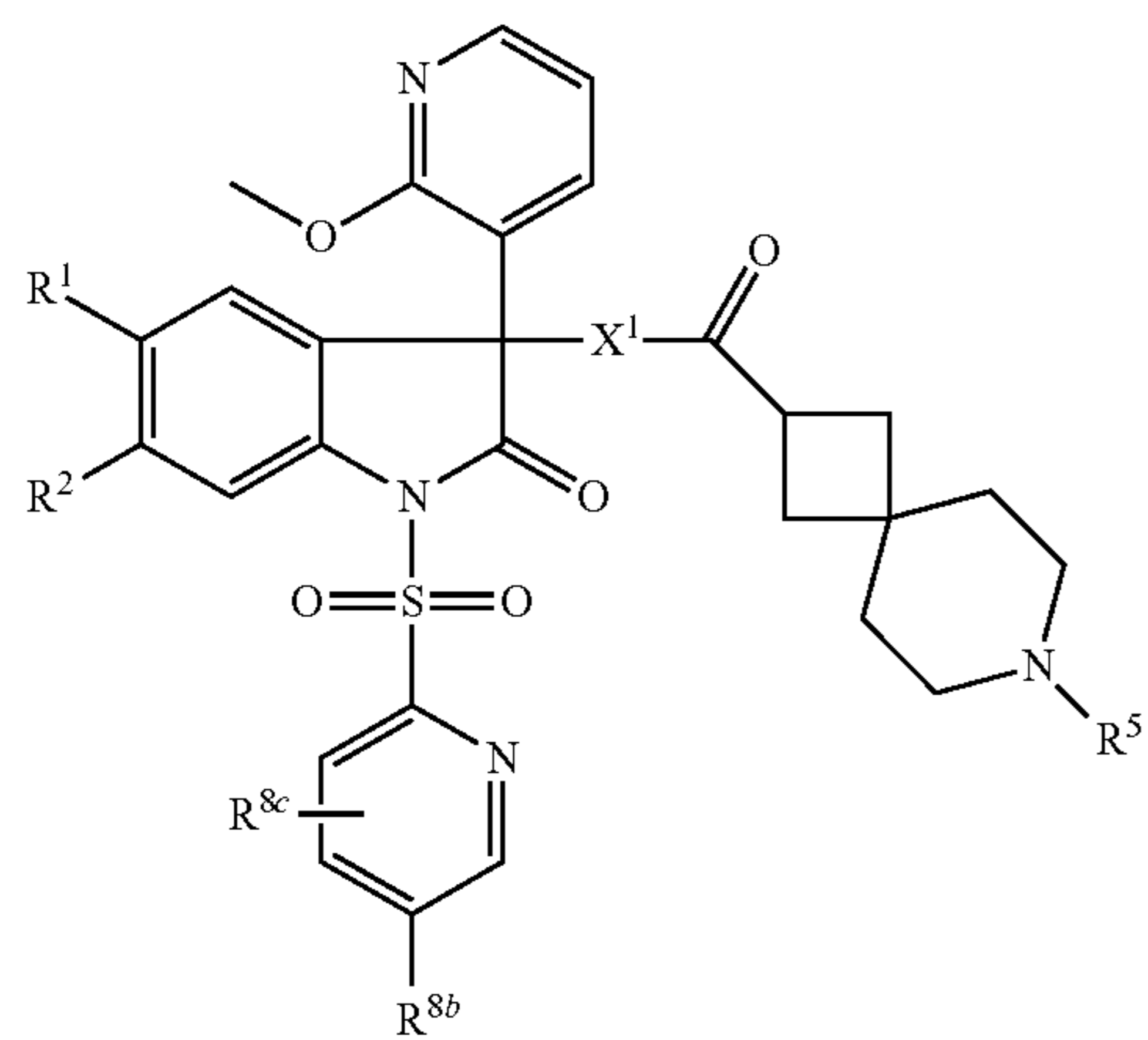


I.86



53

-continued



I.87

5

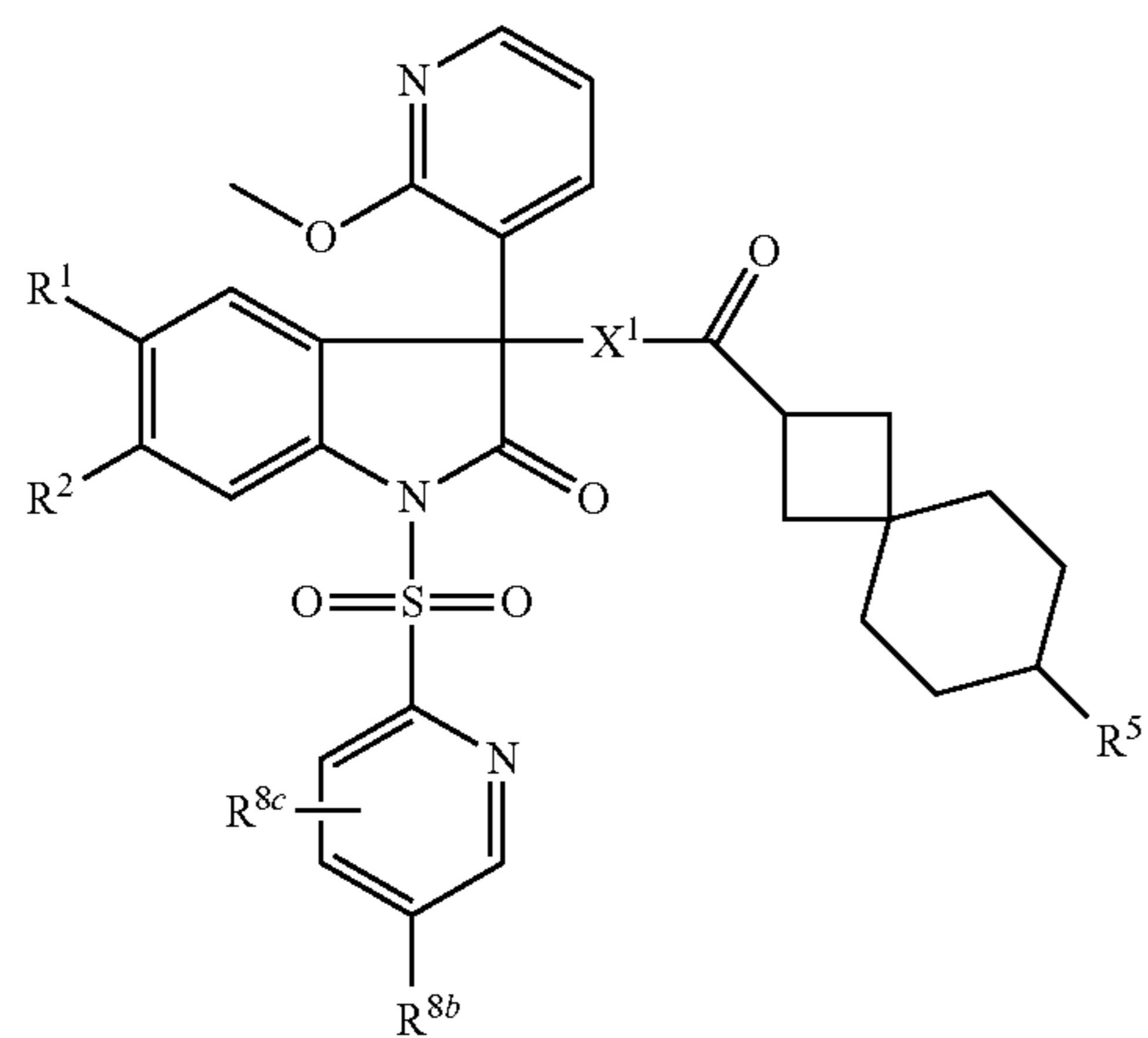
10

15

20

25

I.88



30

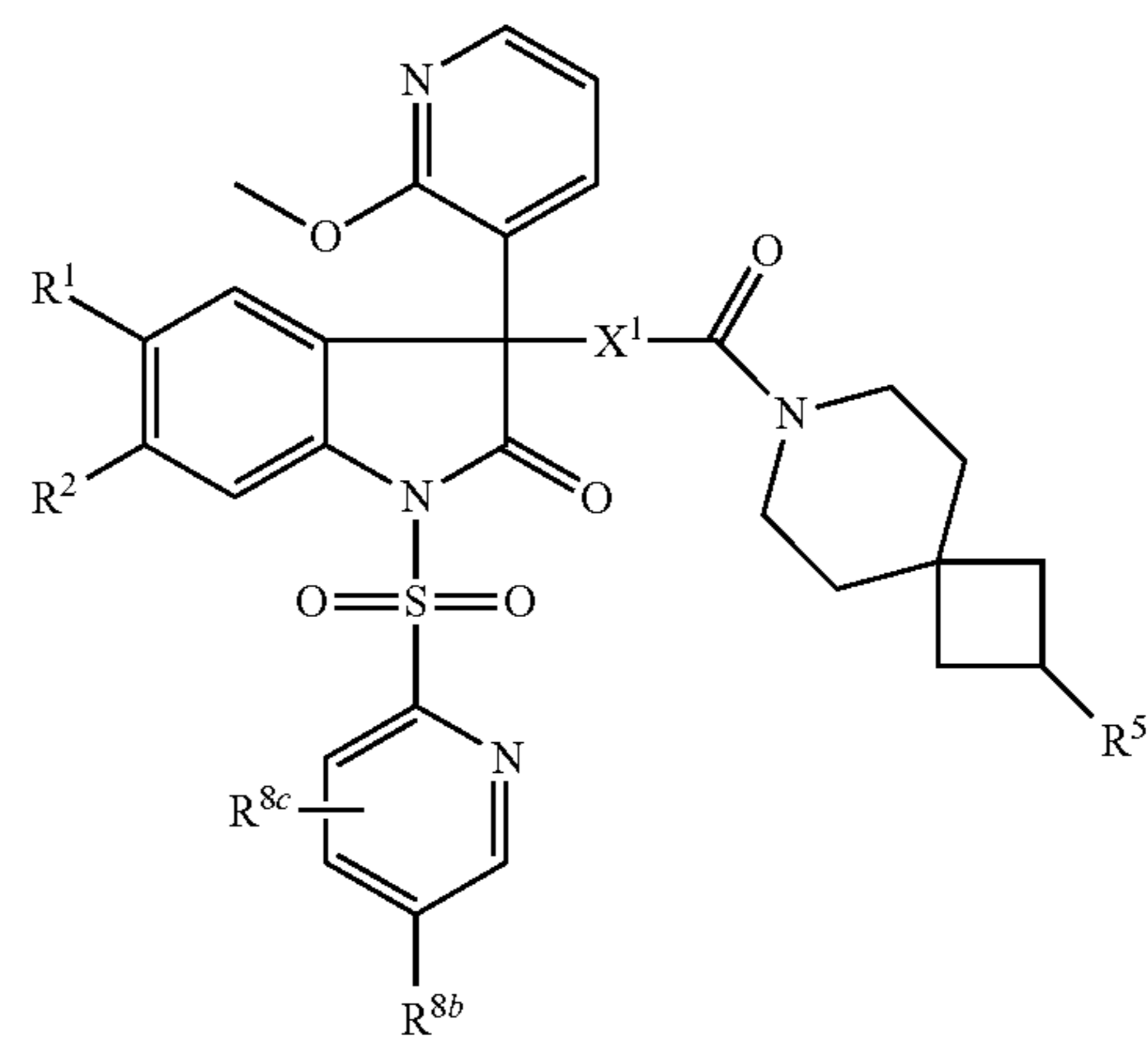
35

40

45

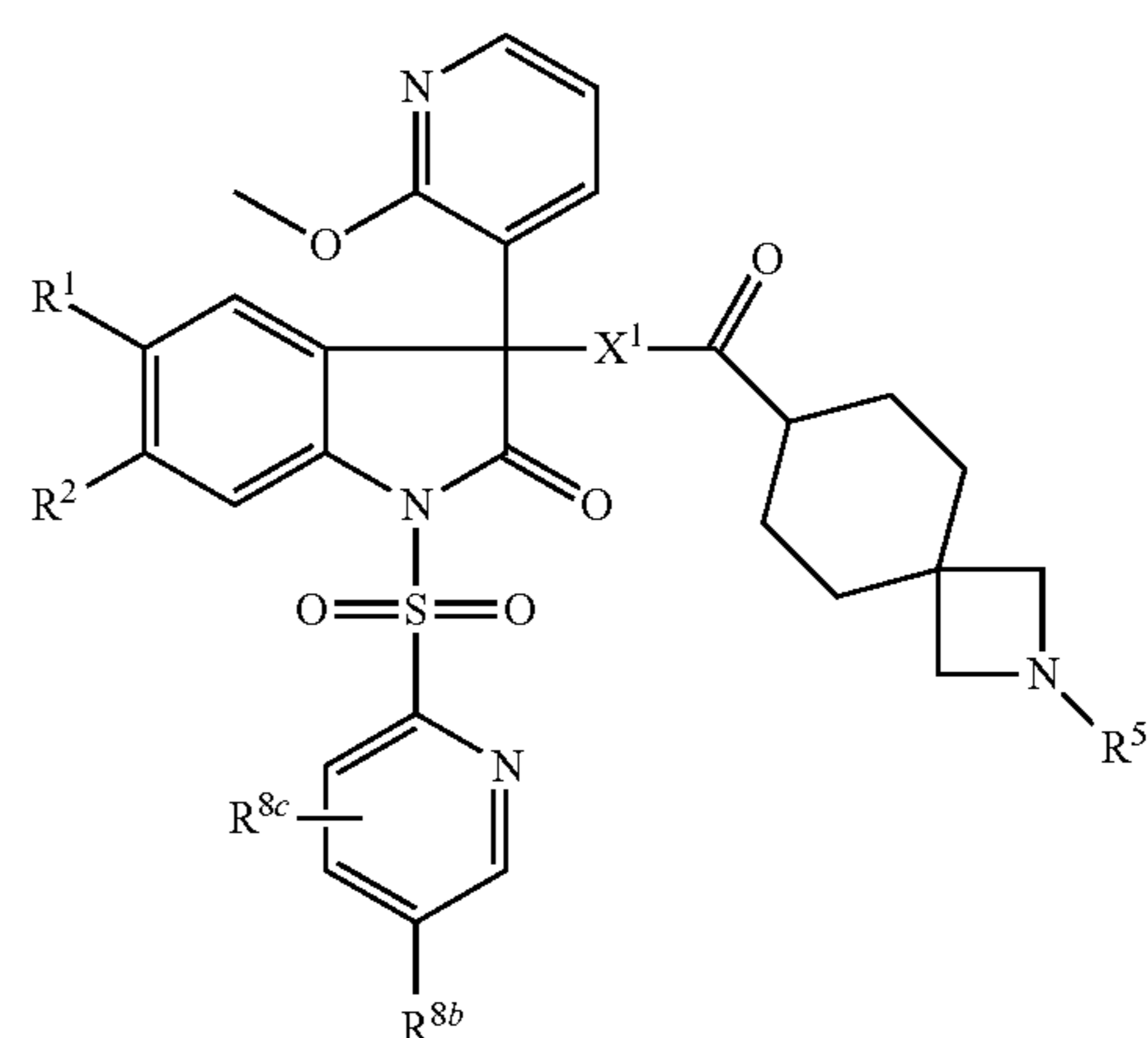
54

-continued



25

I.88



30

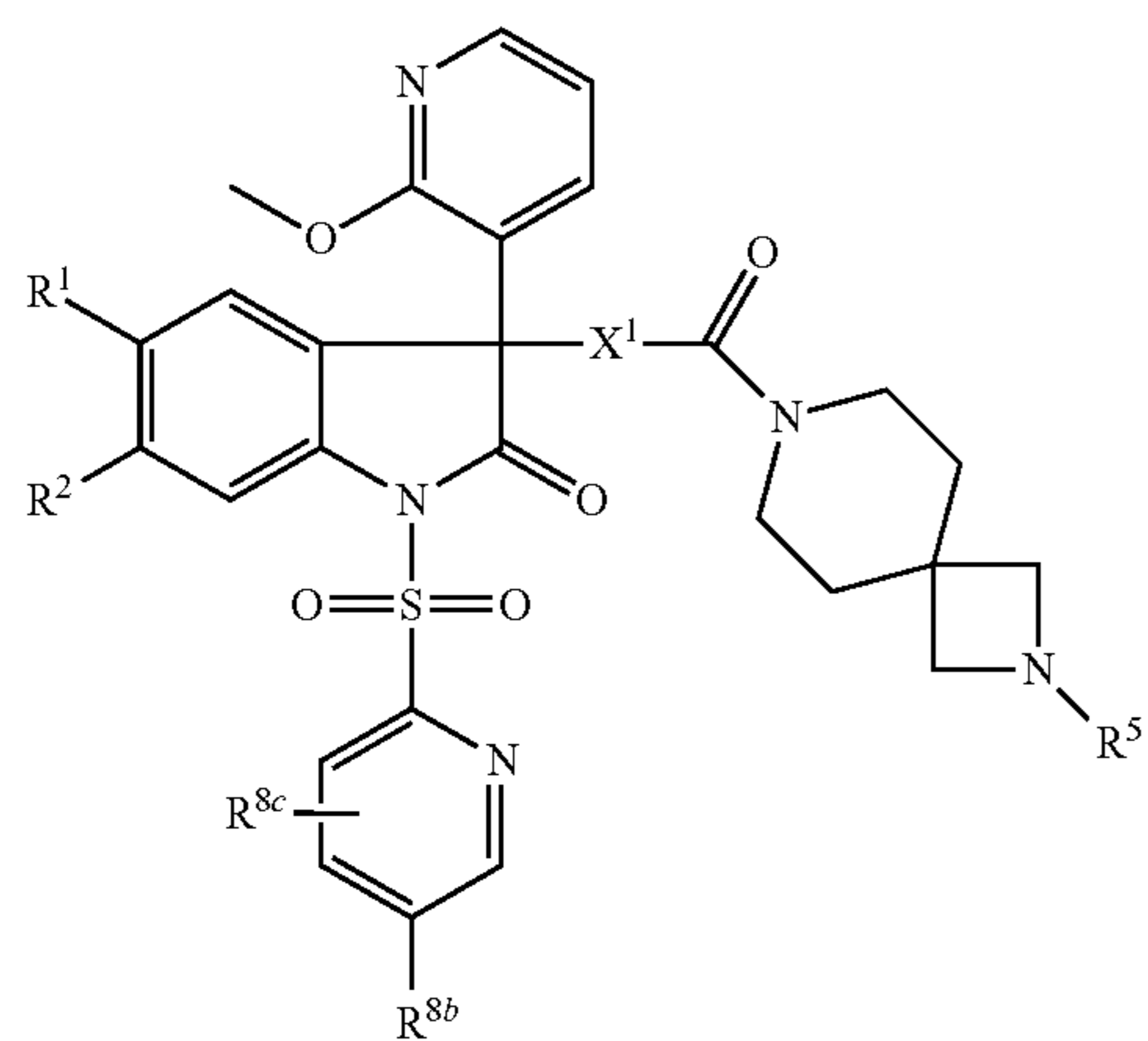
35

40

45

I.89

50



55

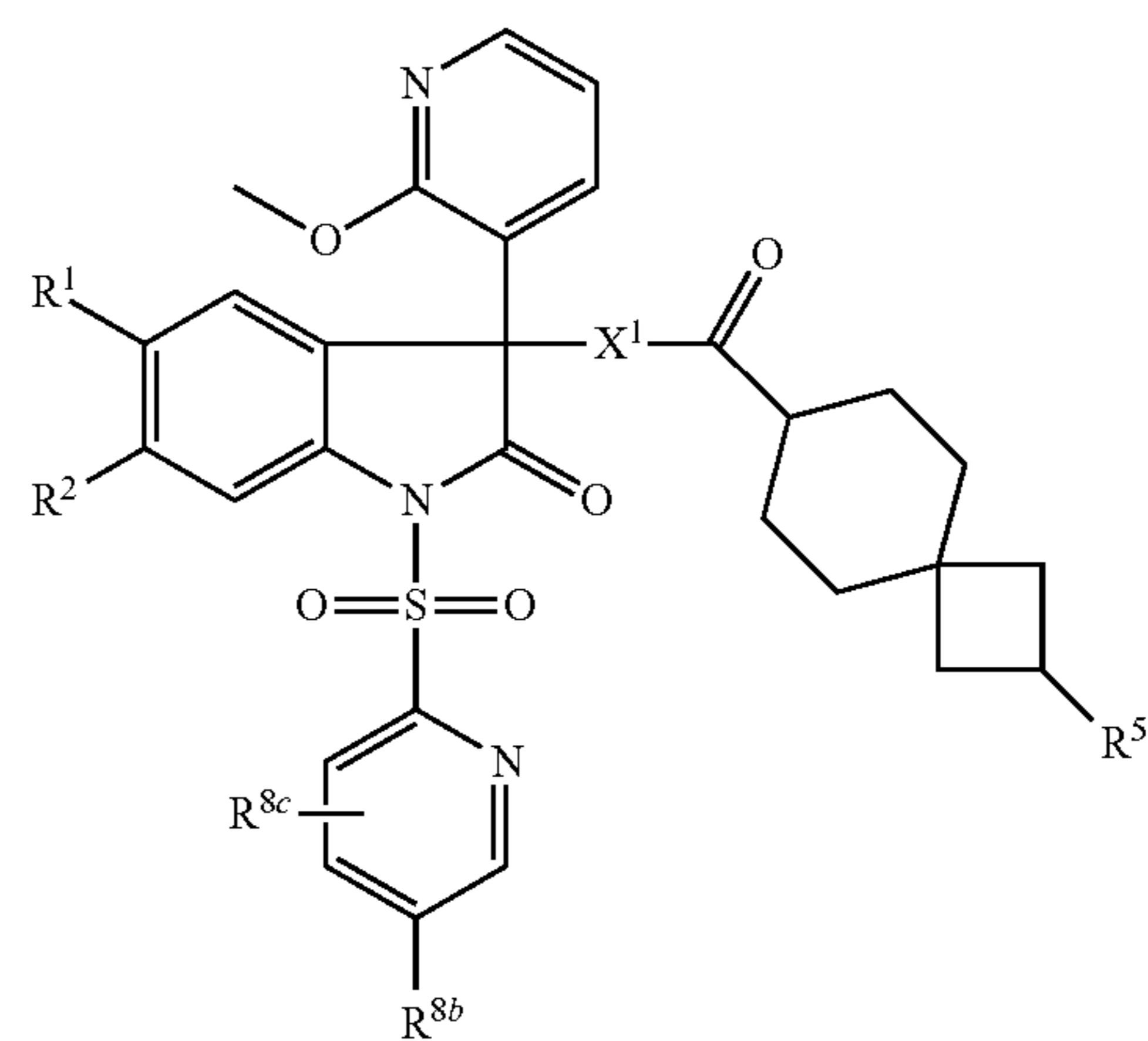
60

65

I.90

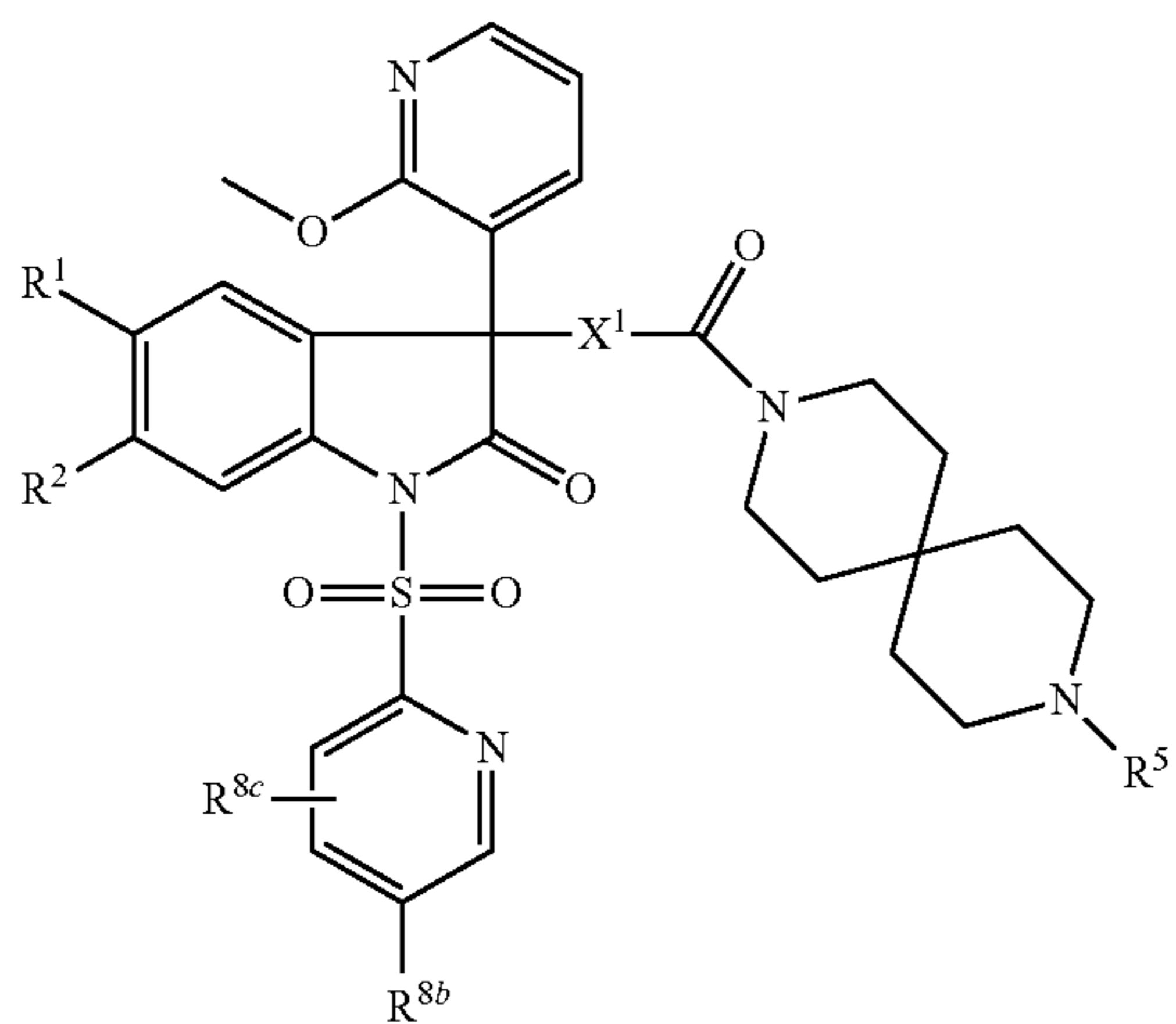
I.91

I.92



55

-continued



I.93

5

10

15

20

25

I.94

30

35

40

45

I.95

50

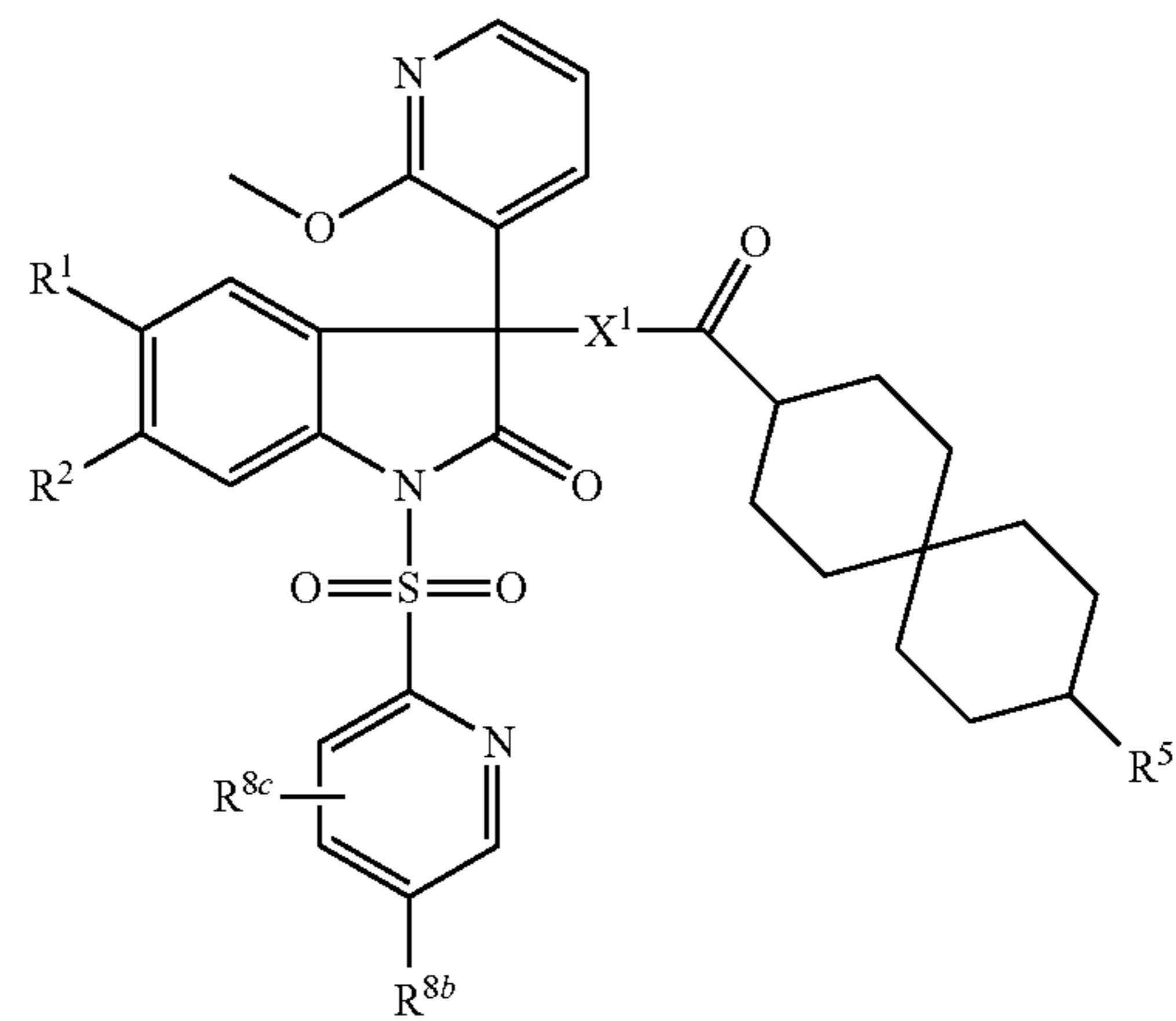
55

60

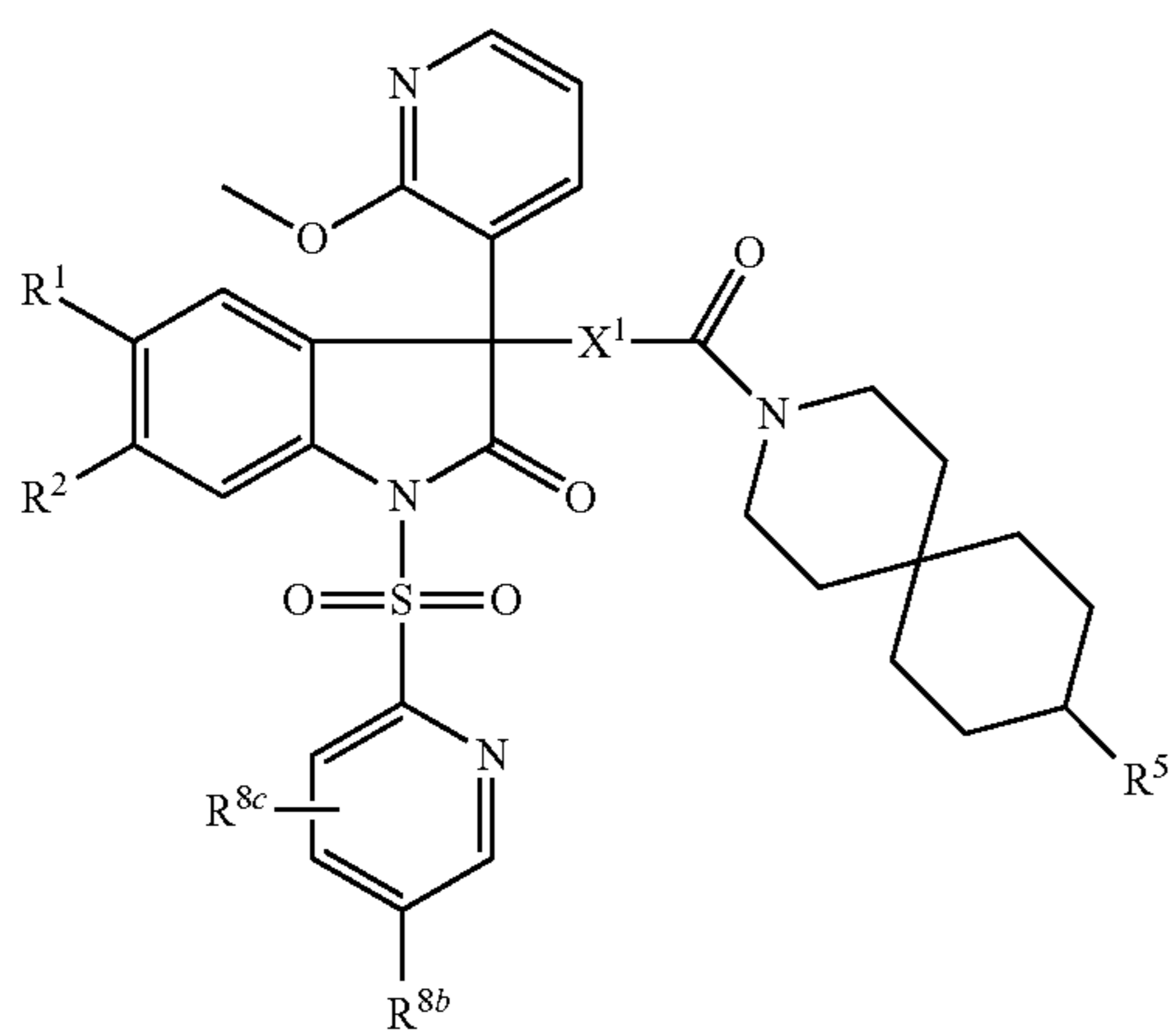
65

56

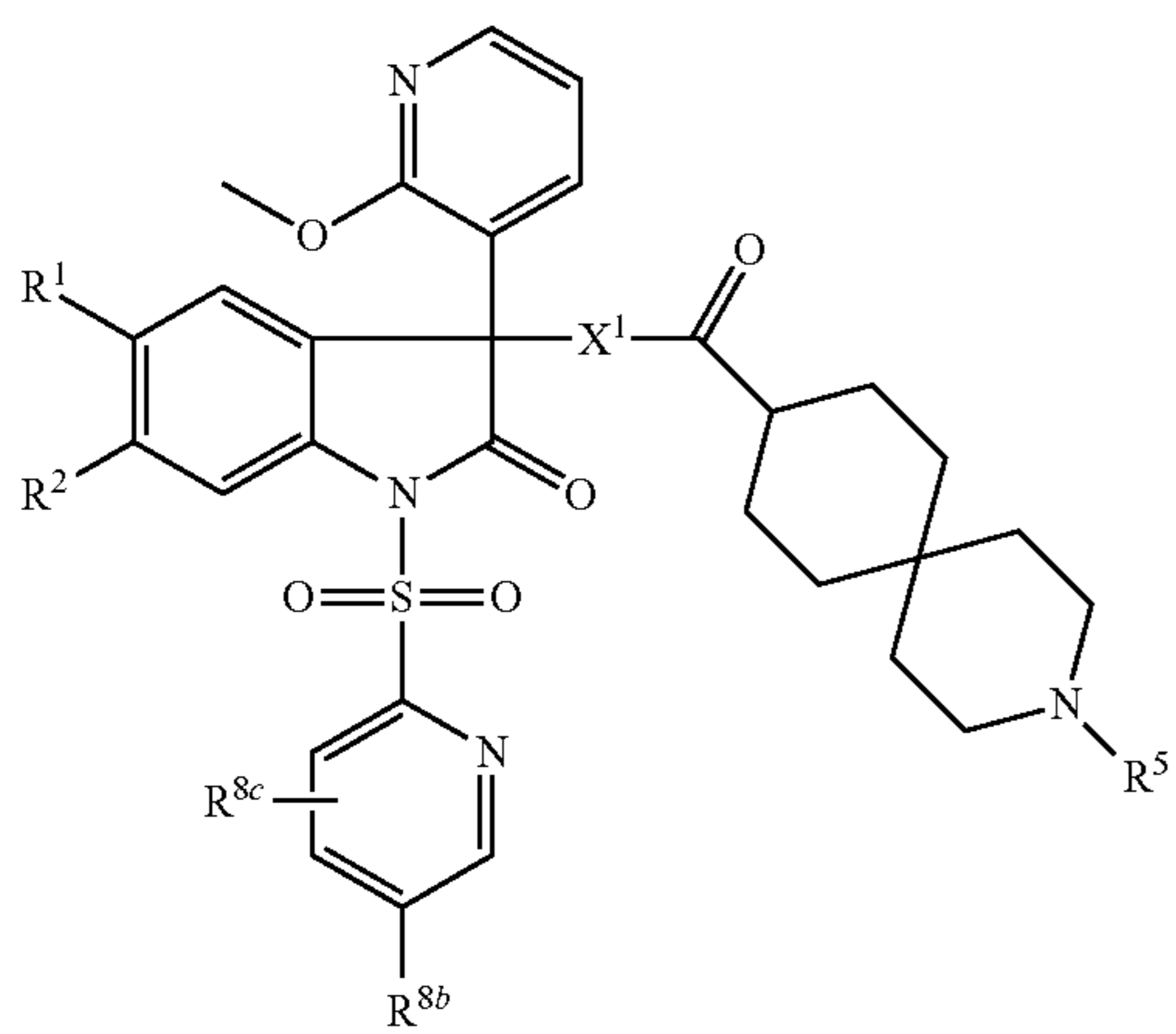
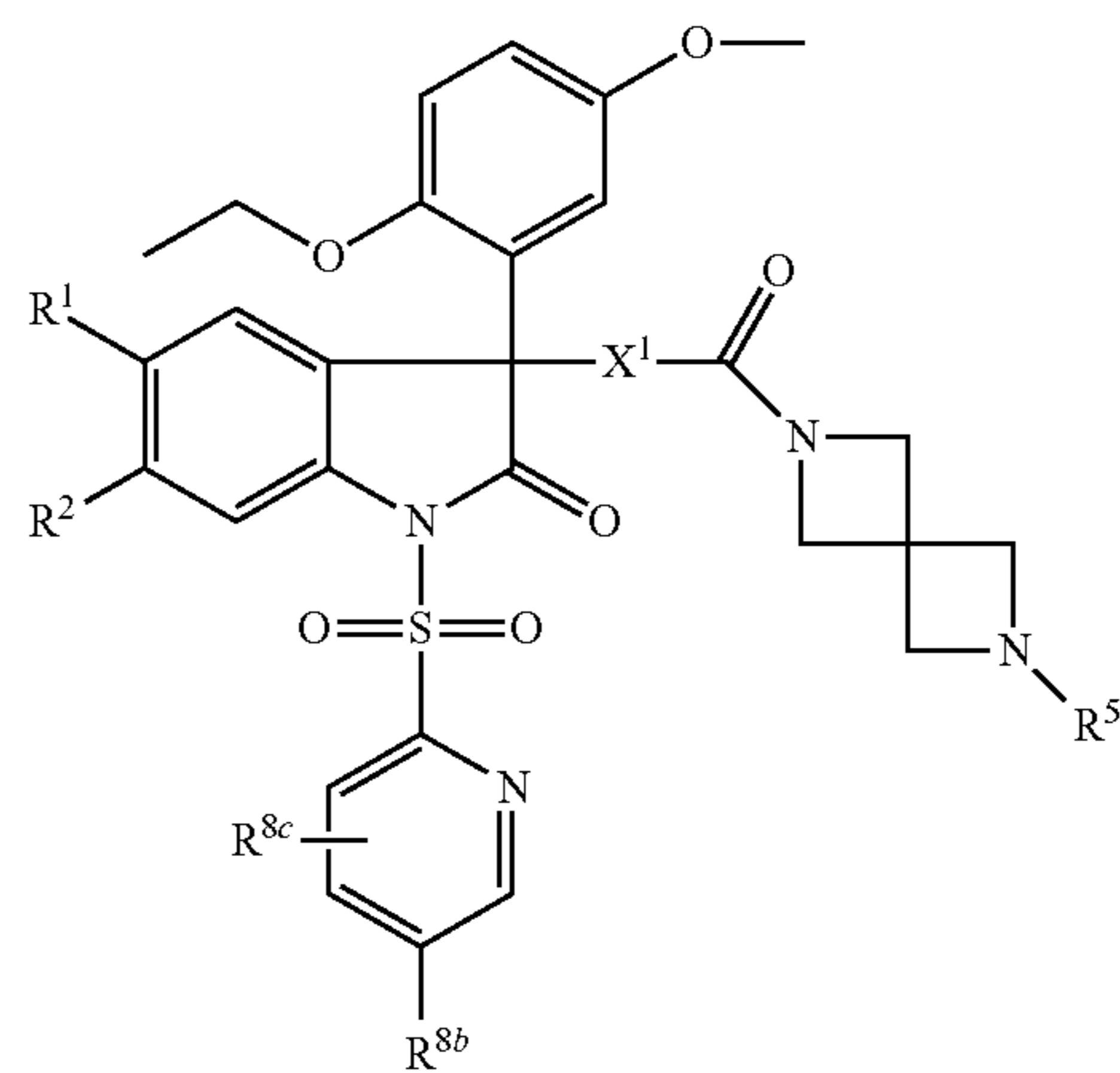
-continued



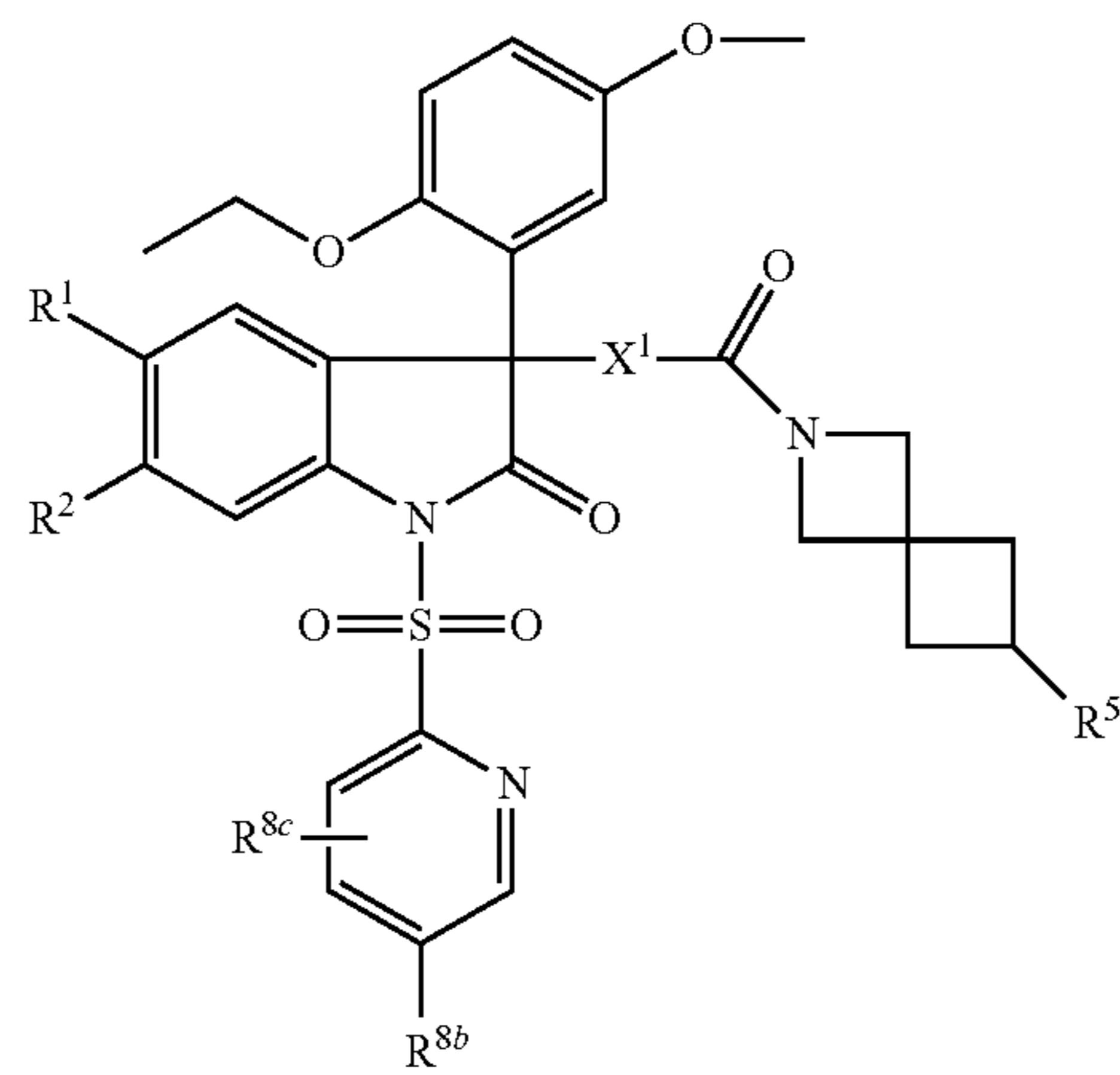
I.96



I.97

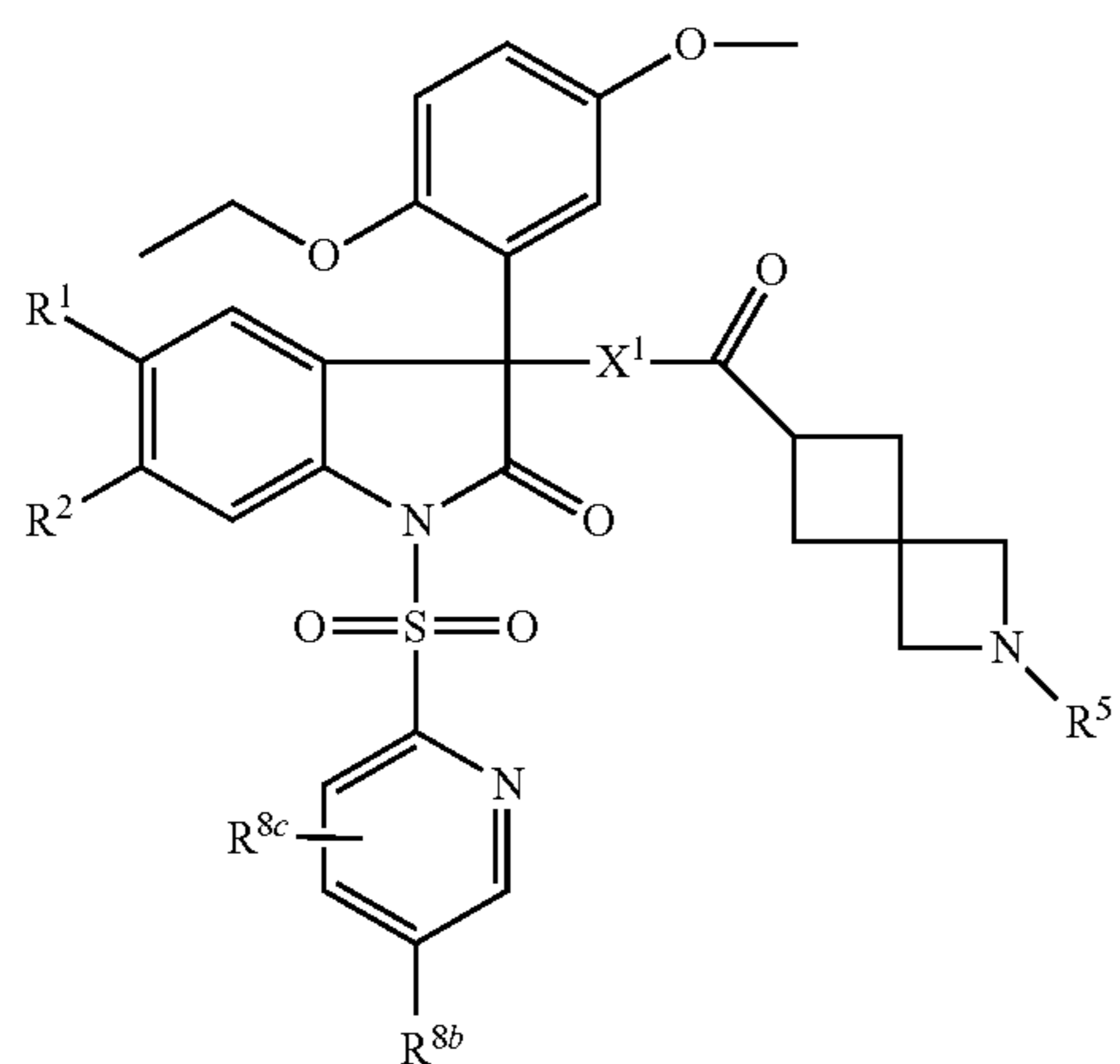


I.98



57

-continued



I.99

5

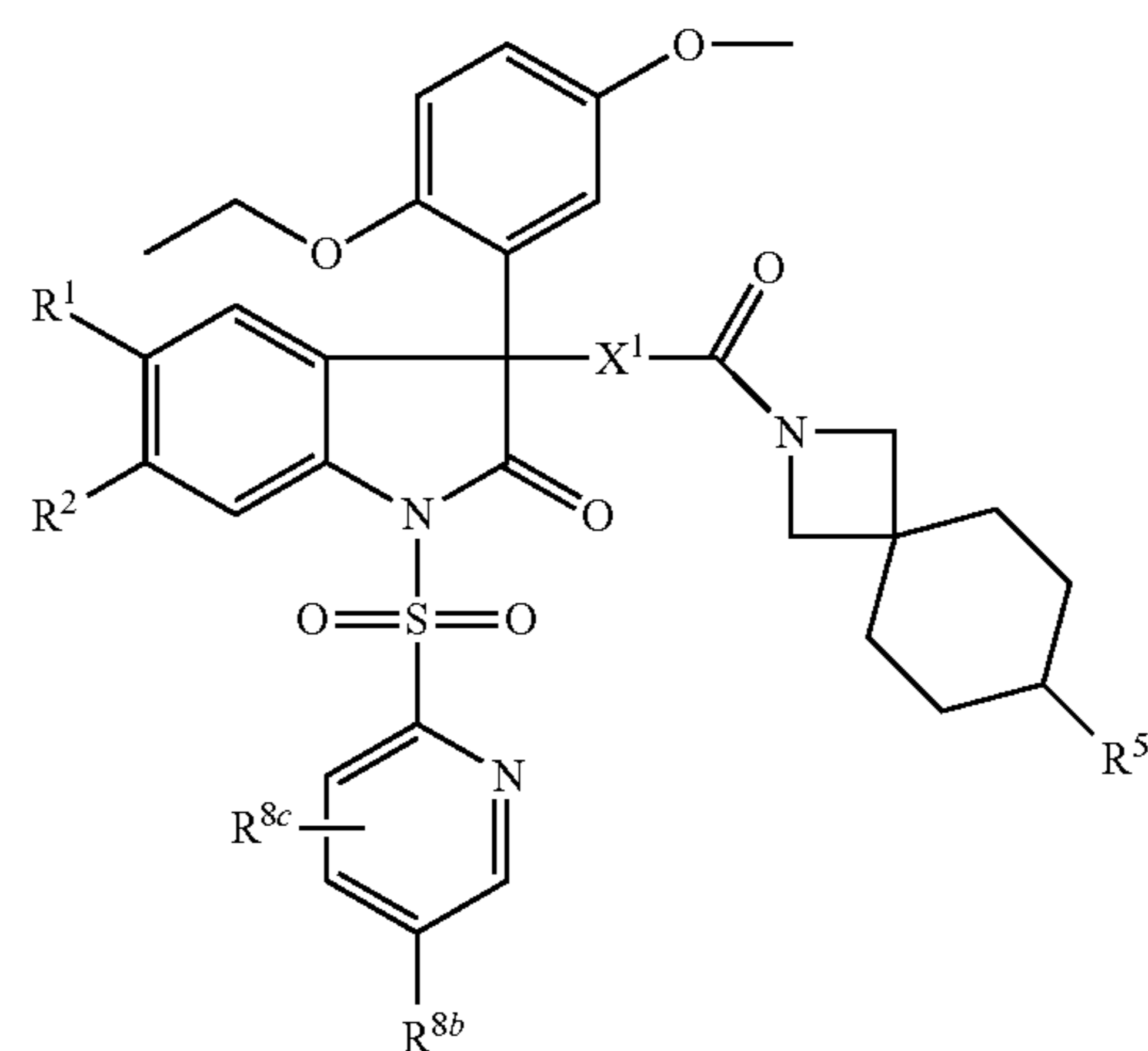
10

15

20

58

-continued



I.102

25

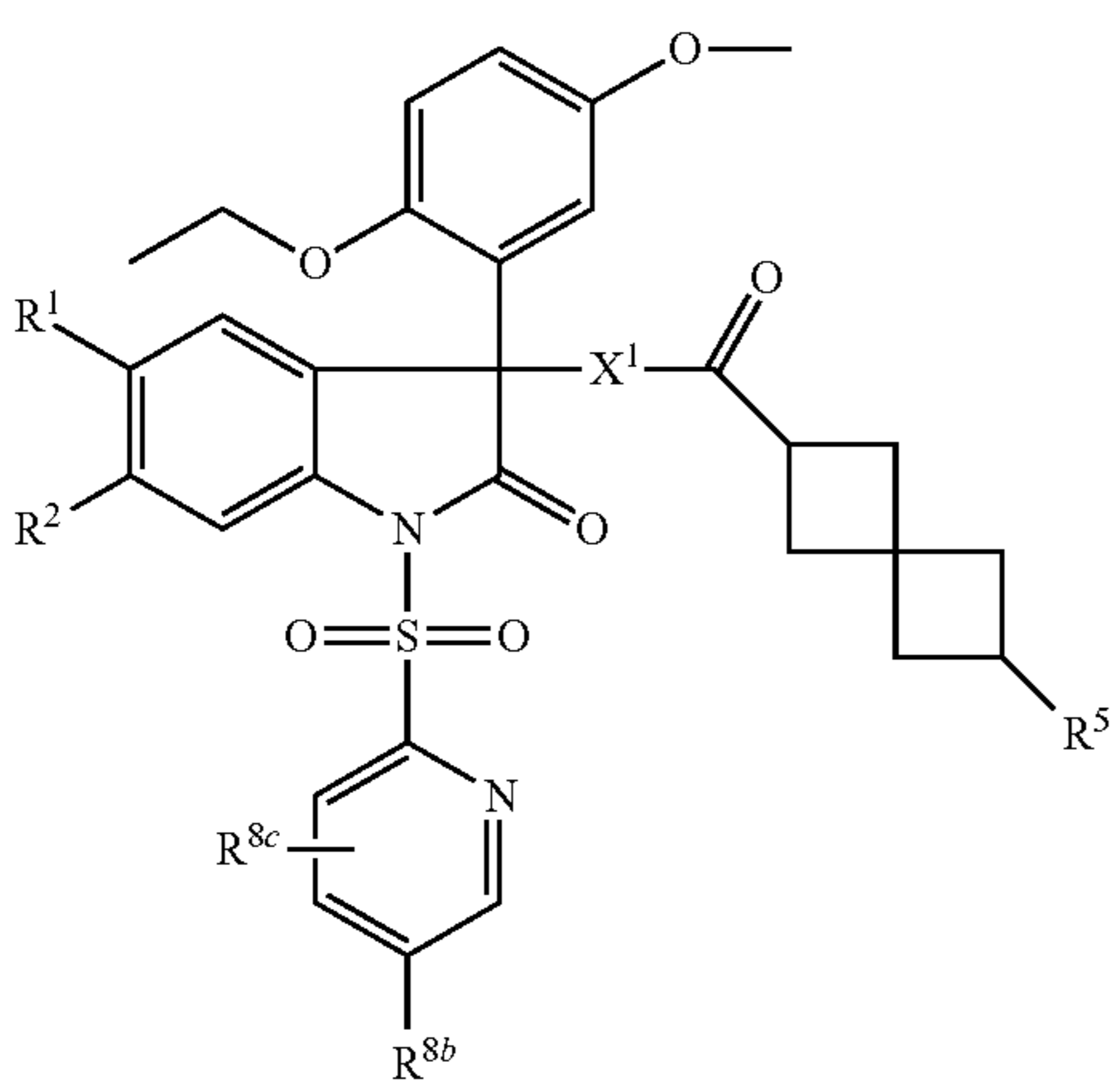
I.100

30

35

40

45



I.103

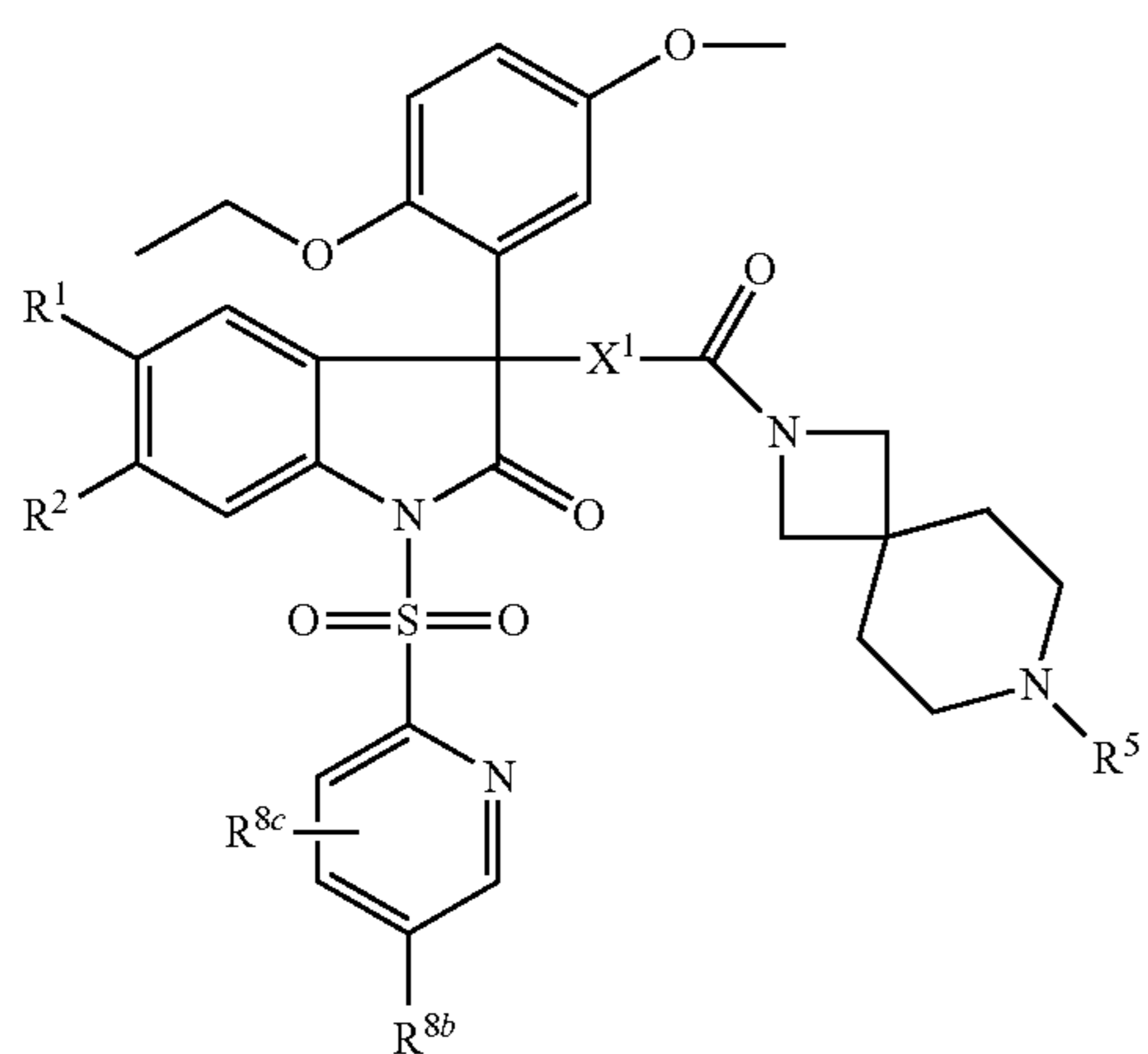
I.101

50

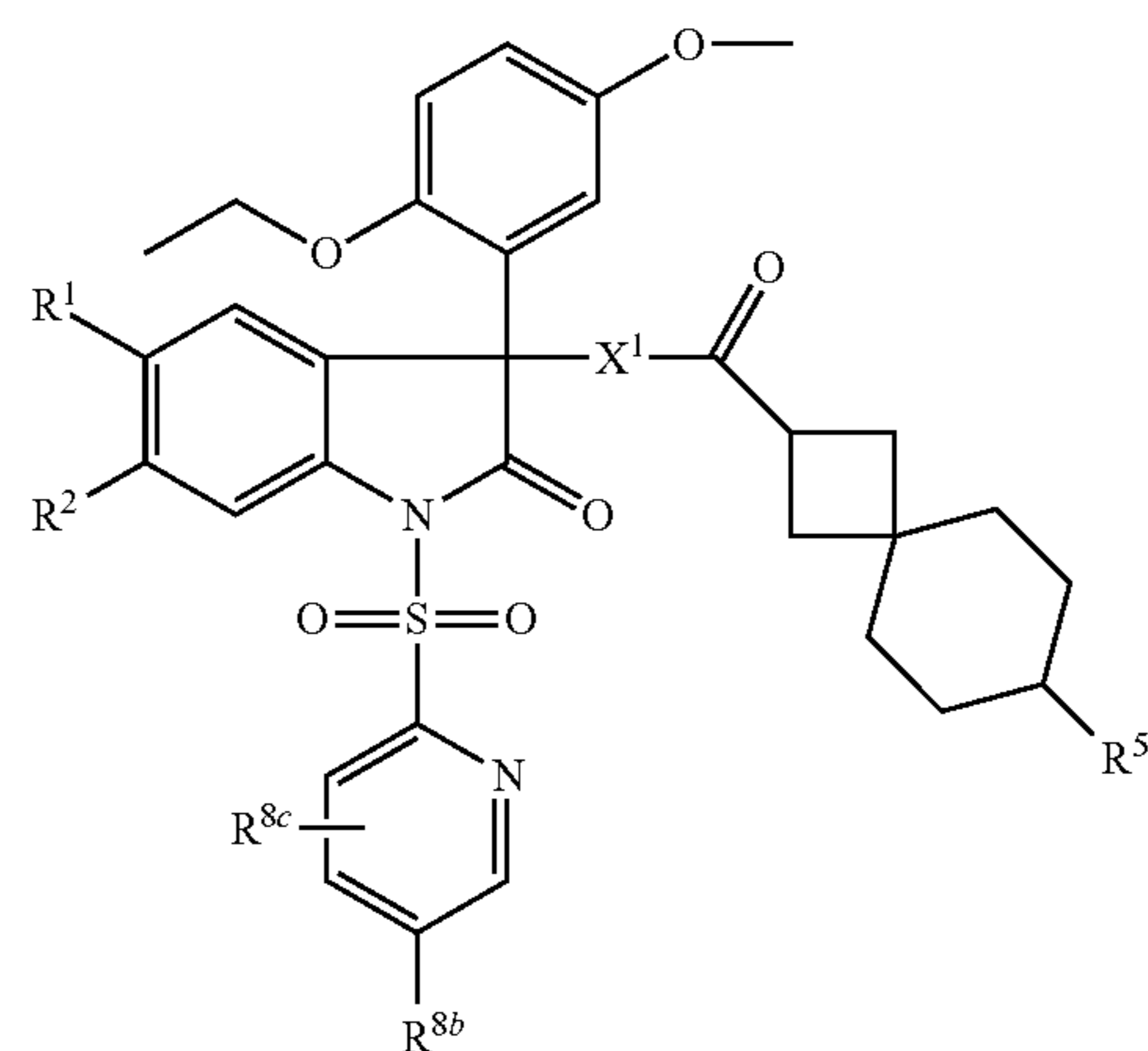
55

60

65

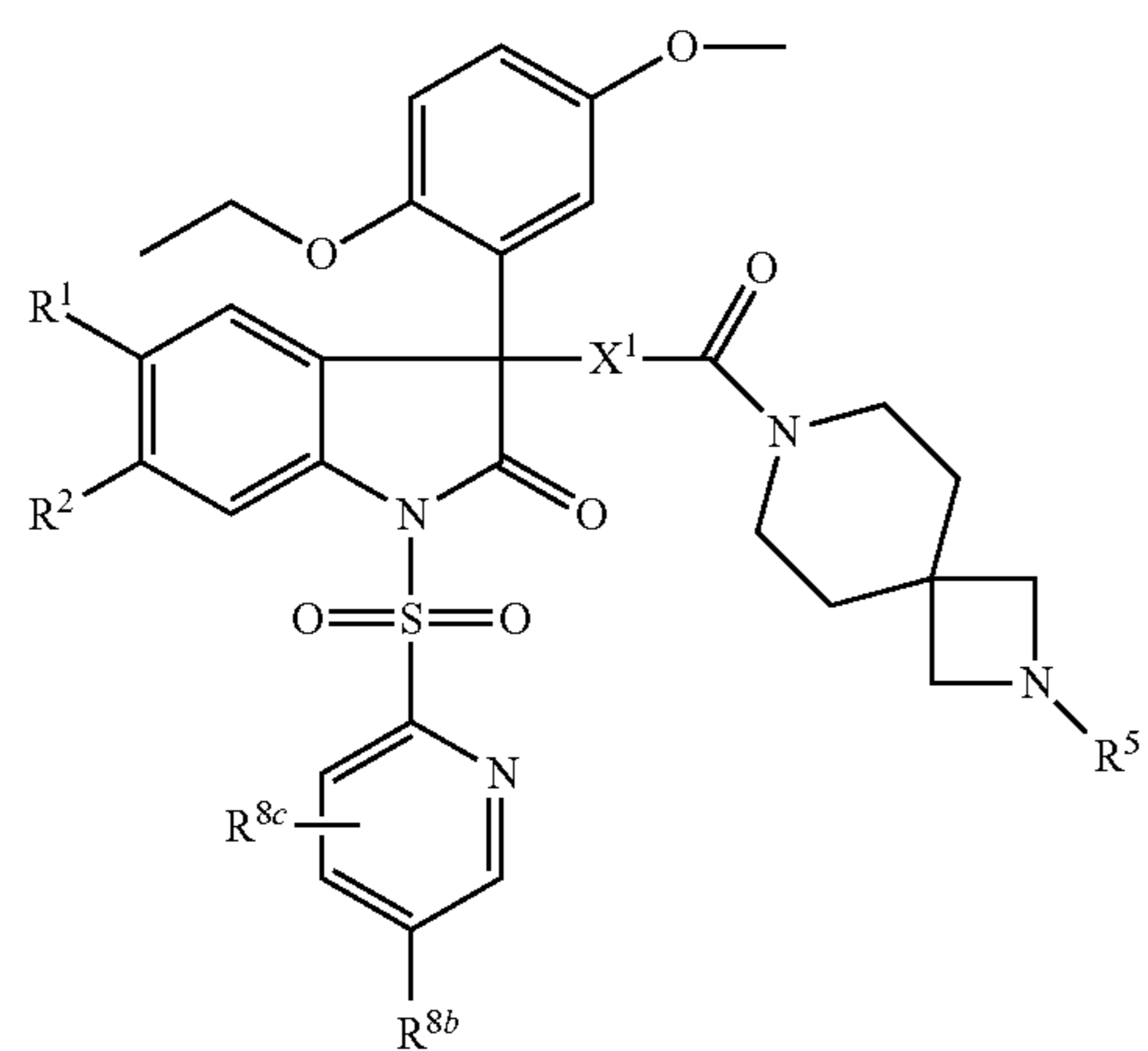


I.104



59

-continued



60

-continued

I.105

I.108

5

10

15

20

25

I.106

I.109

30

35

40

45

I.107

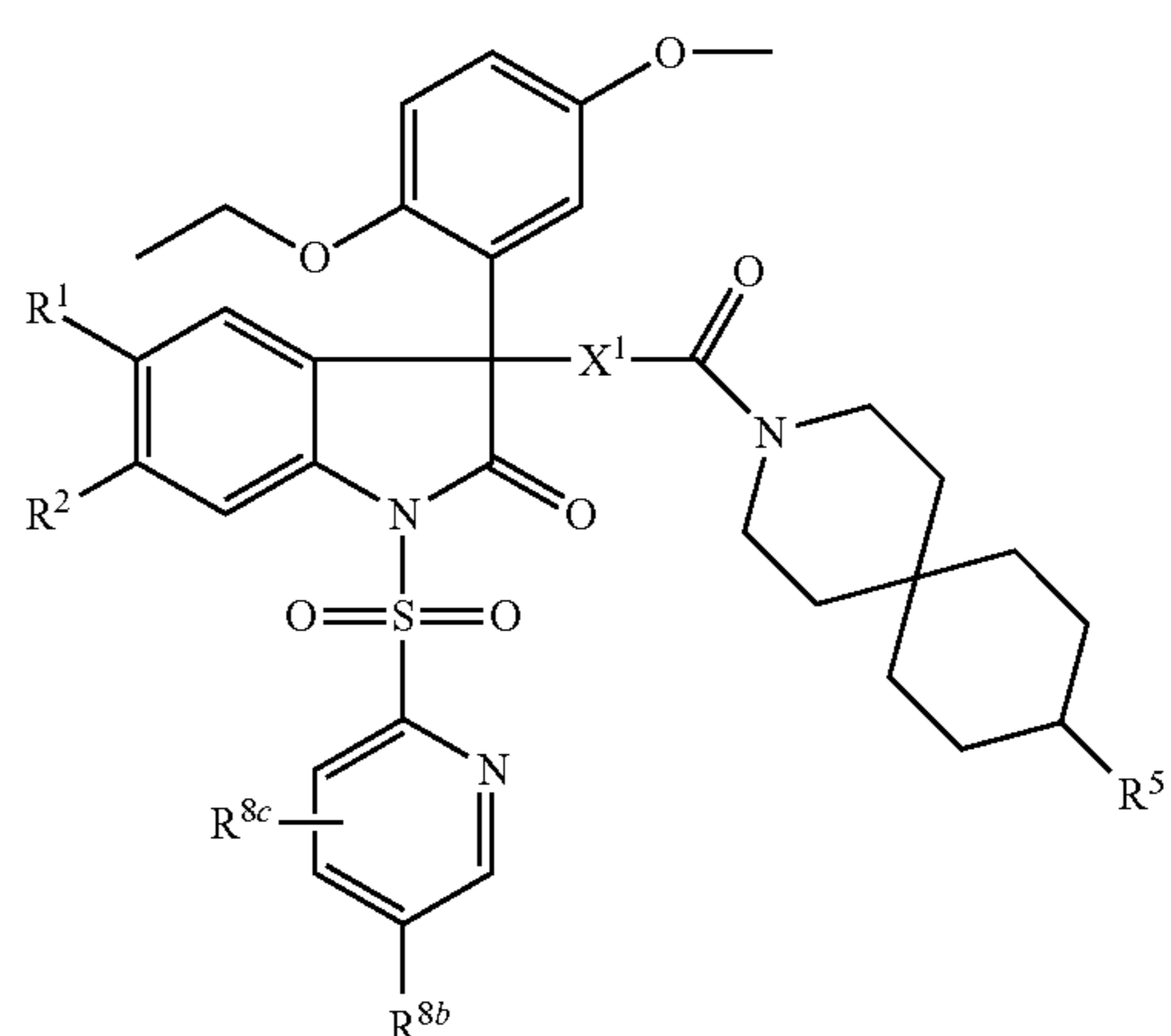
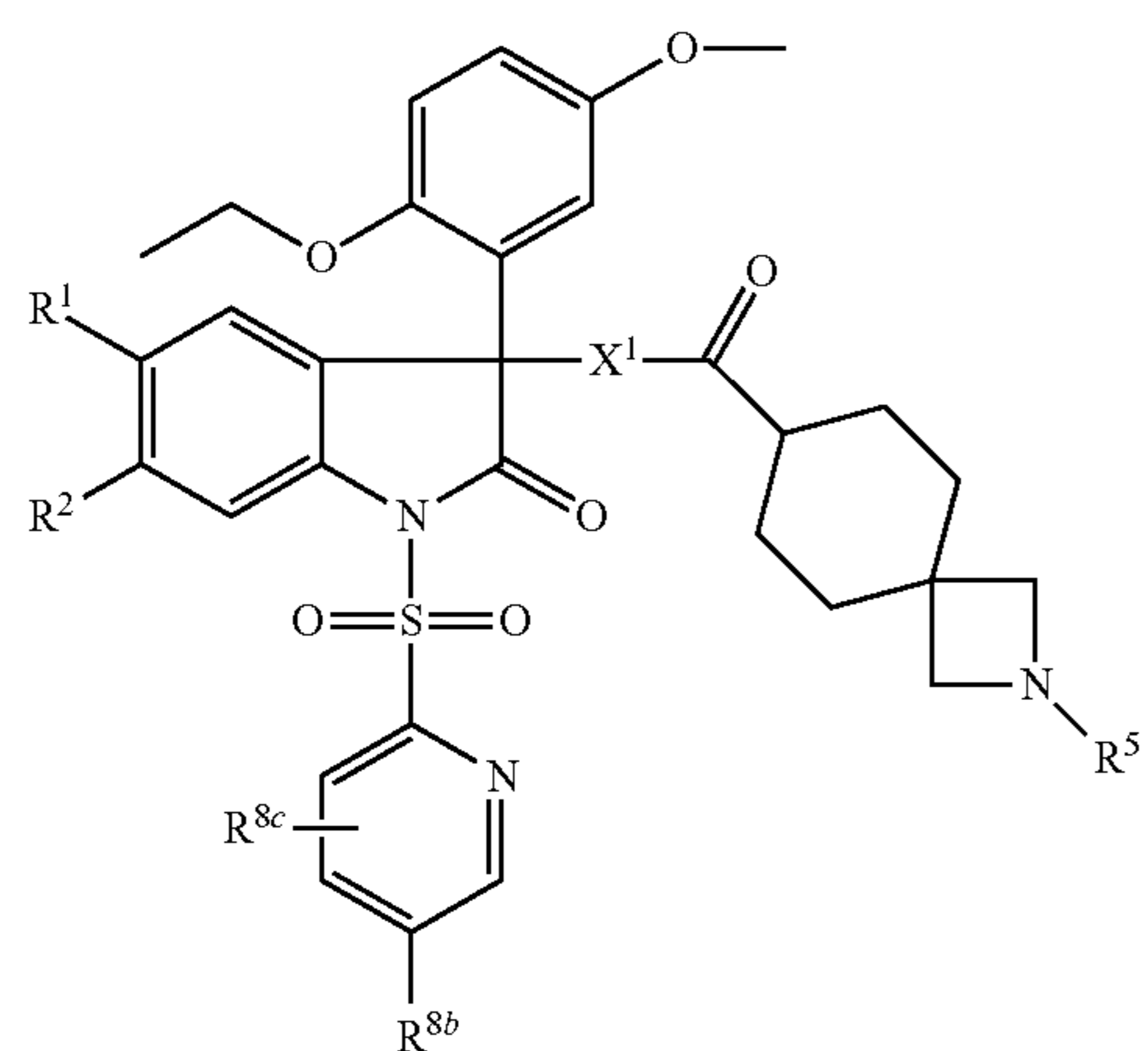
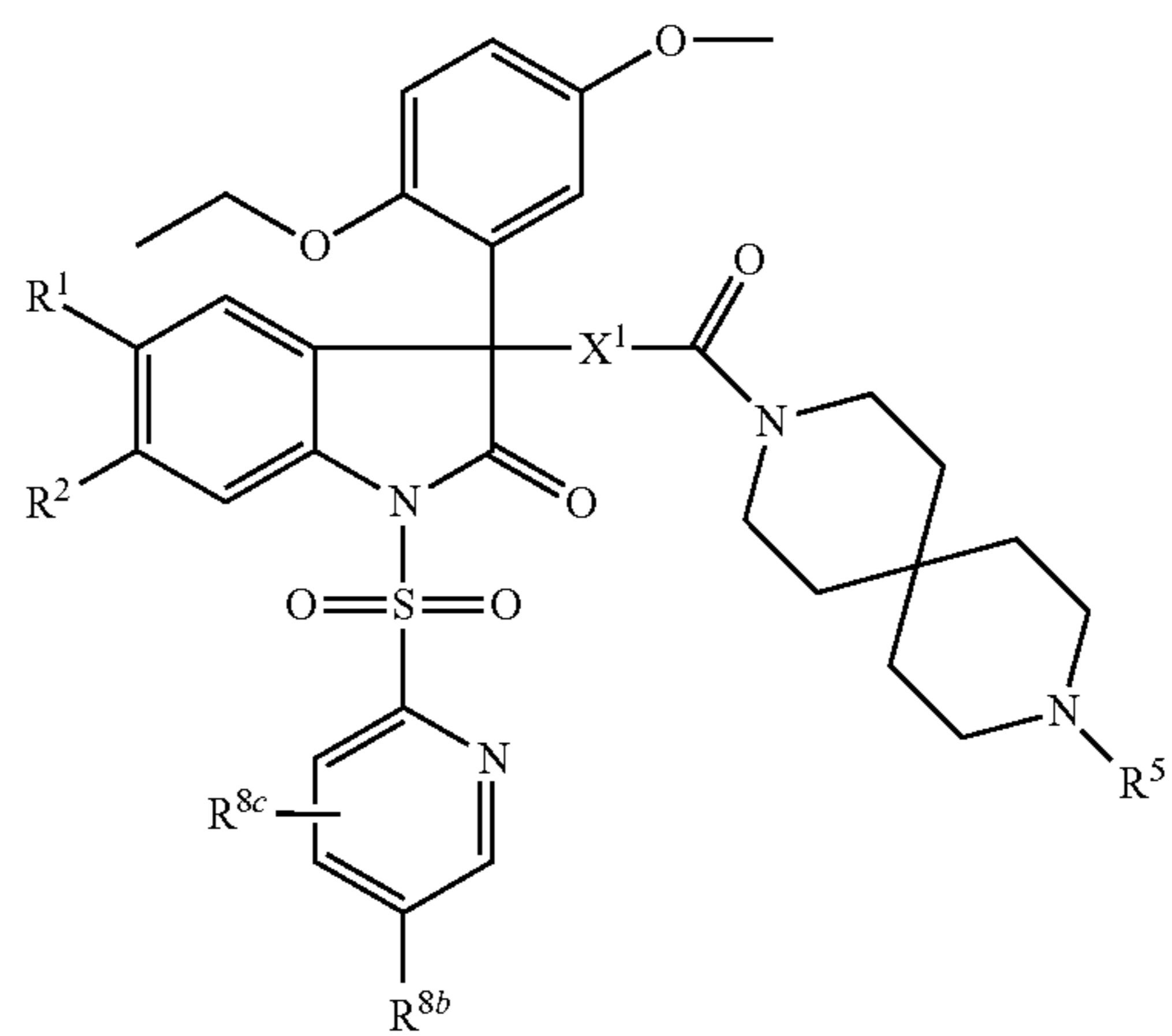
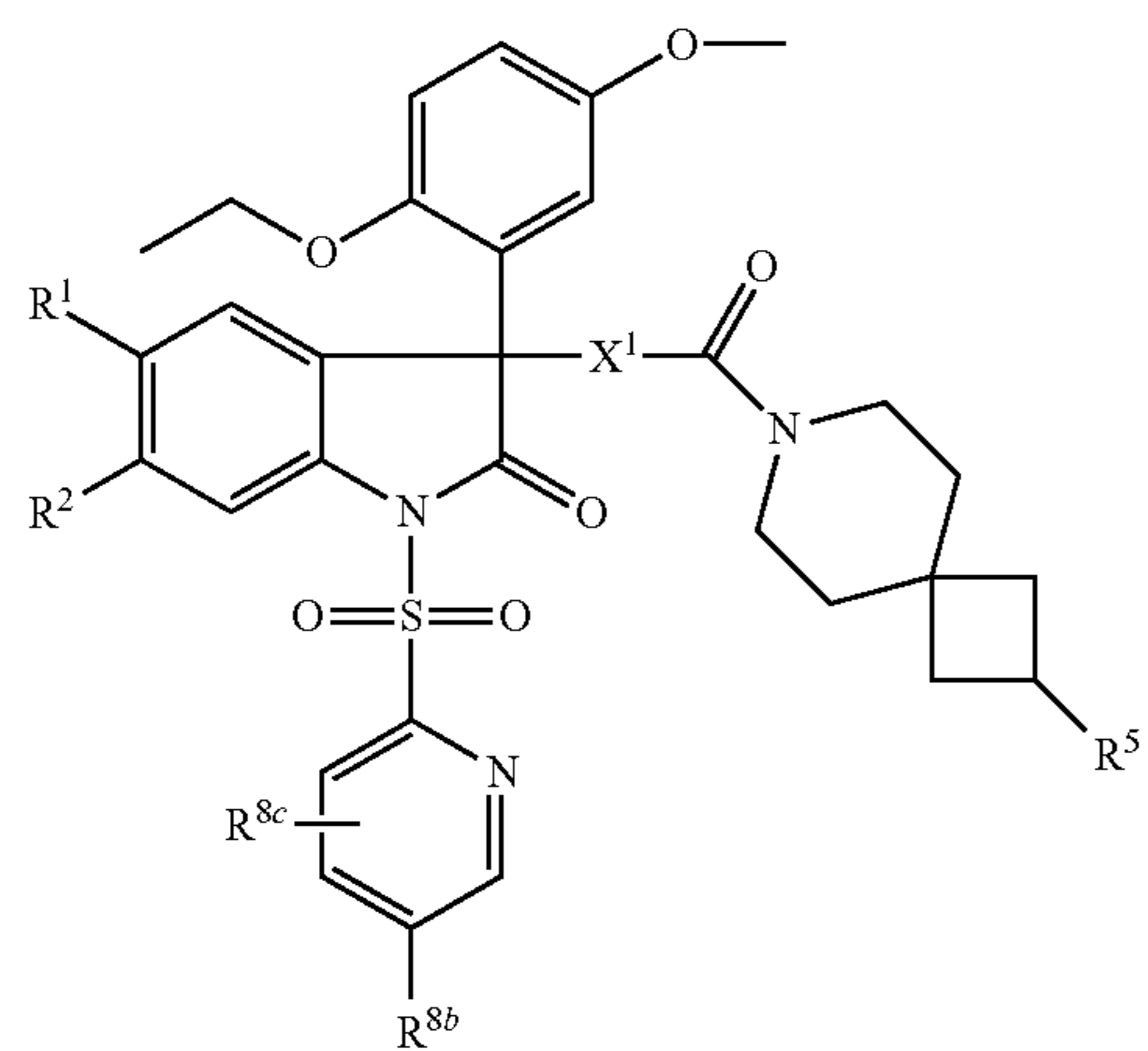
I.110

50

55

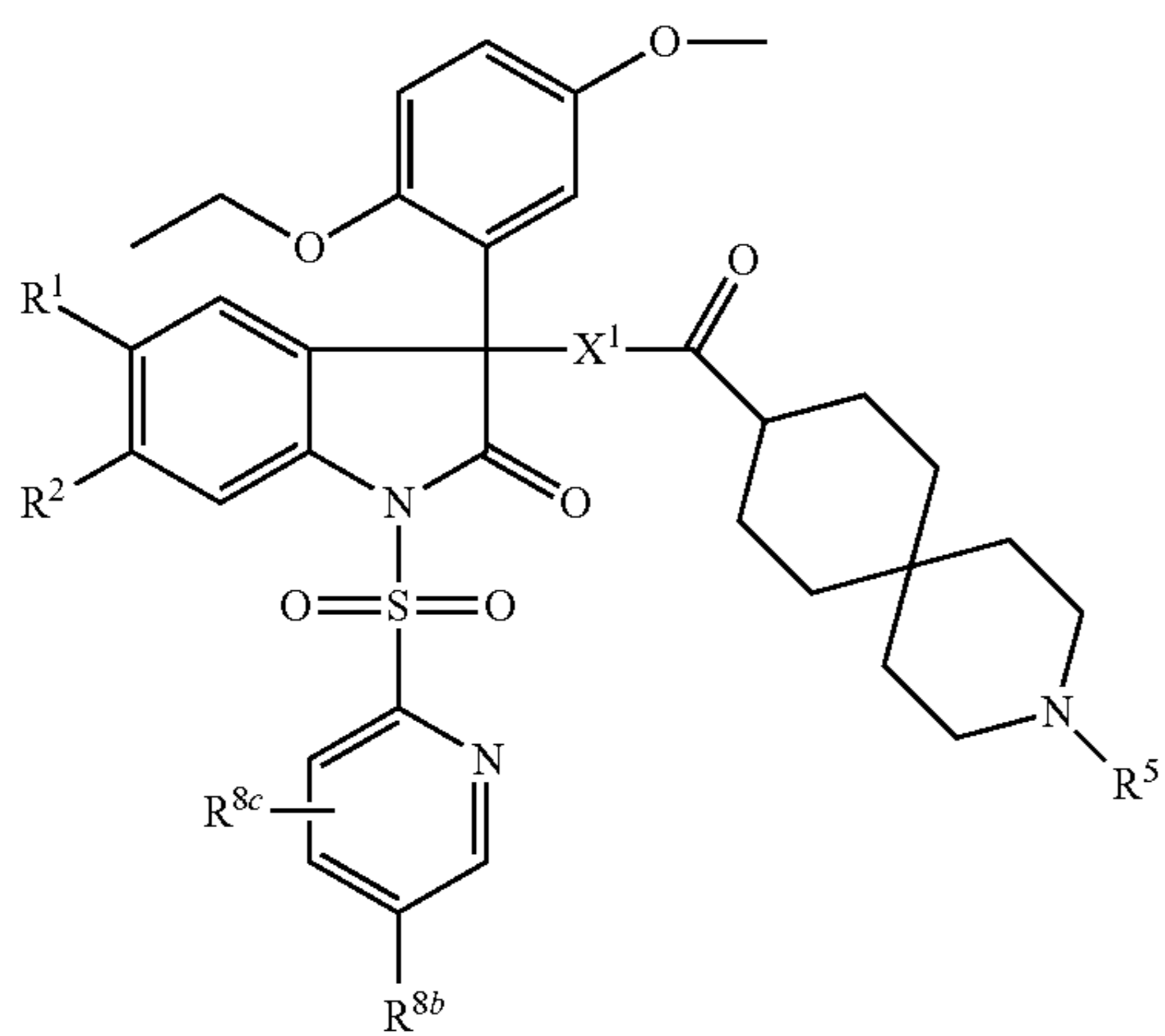
60

65



61

-continued



I.111

5

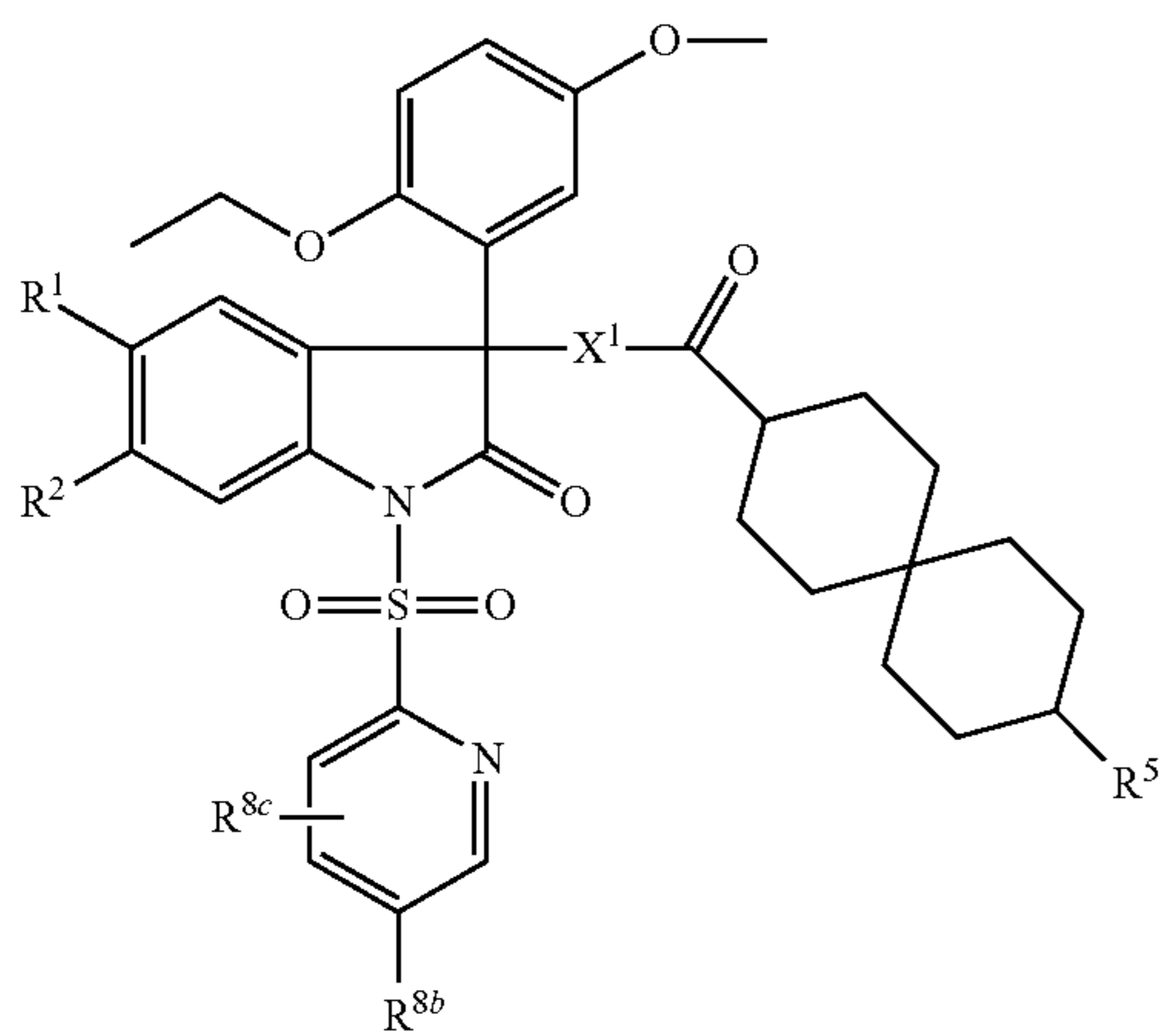
10

15

20

25

I.112



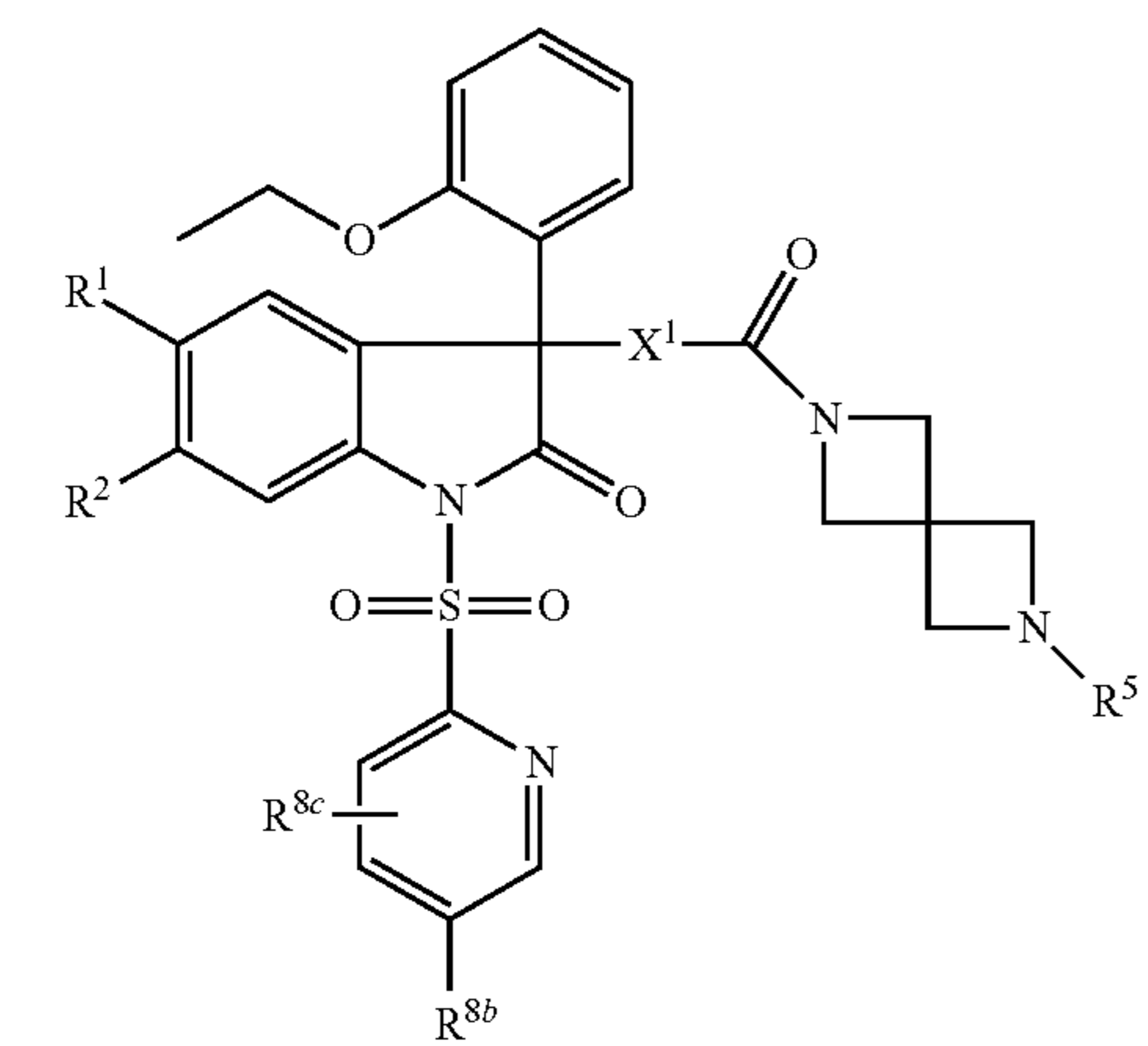
30

35

40

45

I.113



50

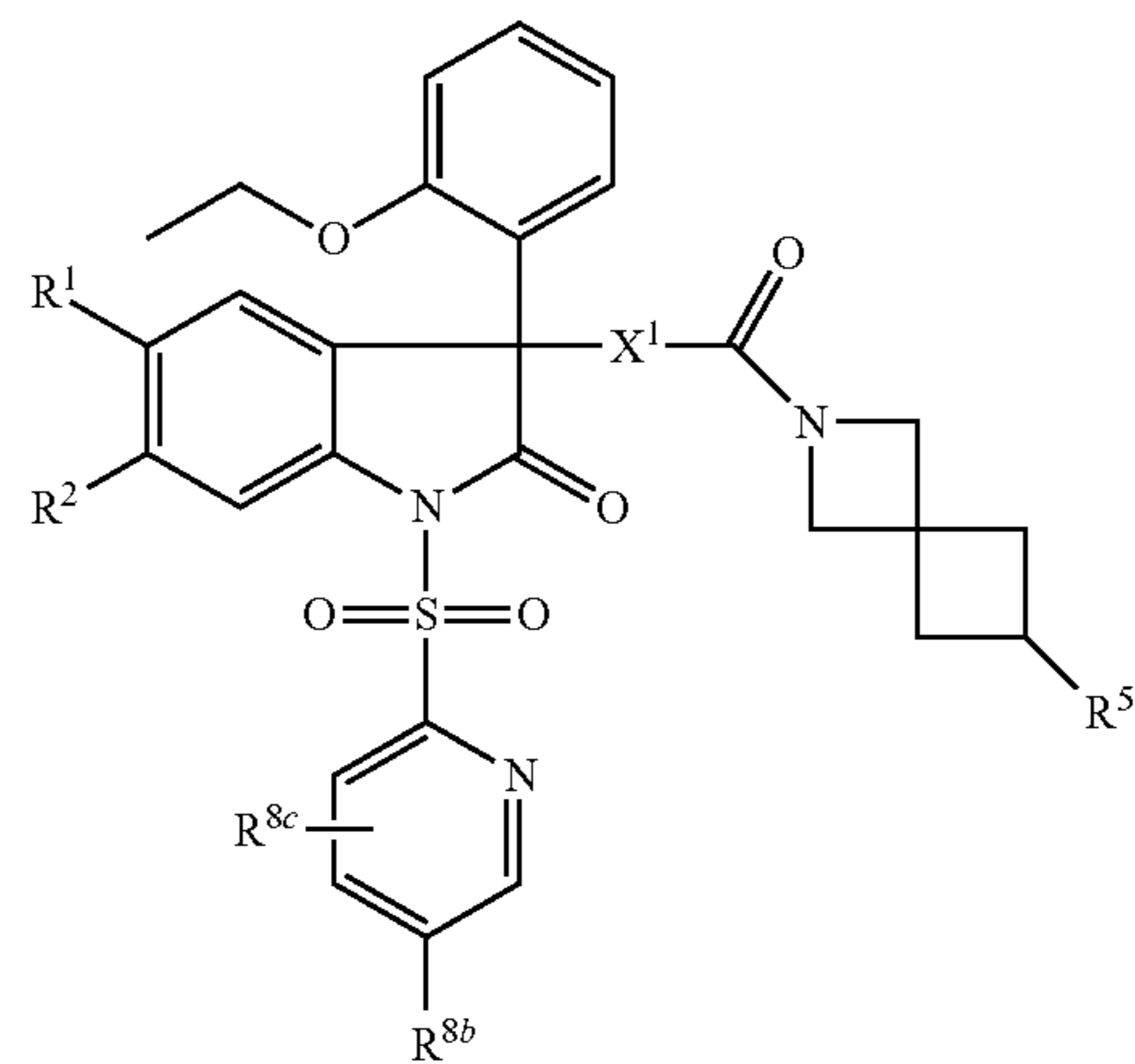
55

60

65

62

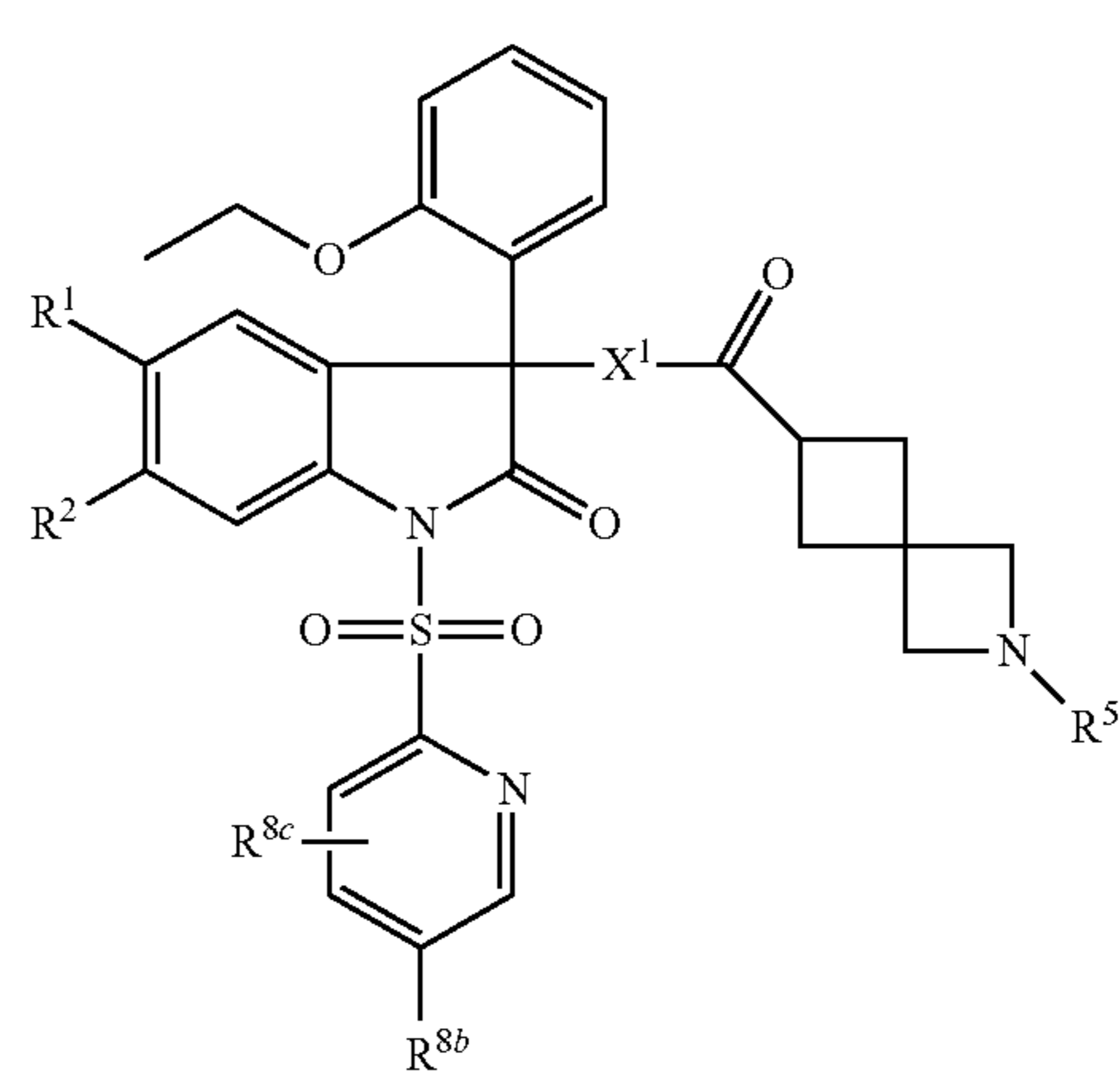
-continued



I.114

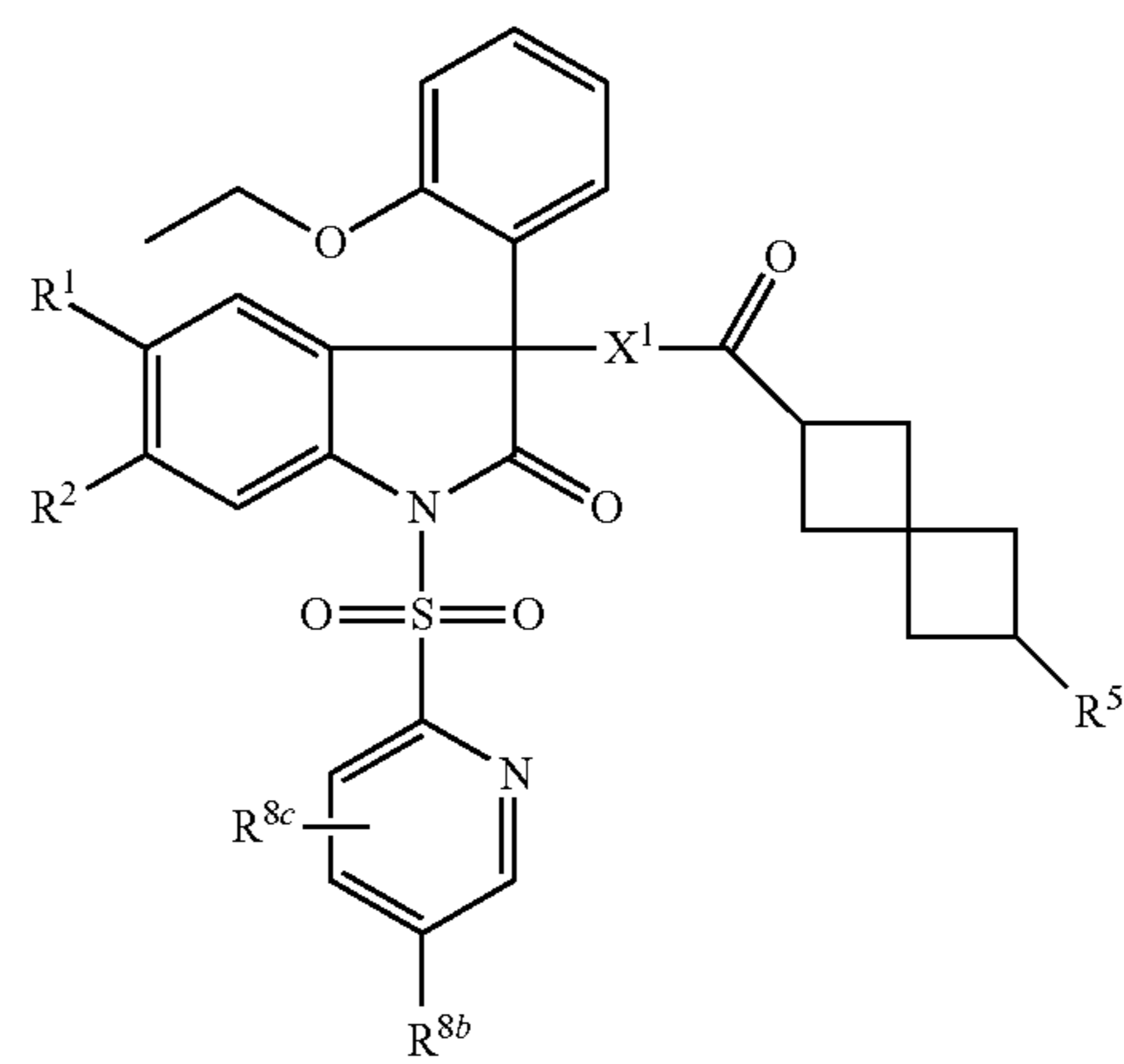
25

I.115



45

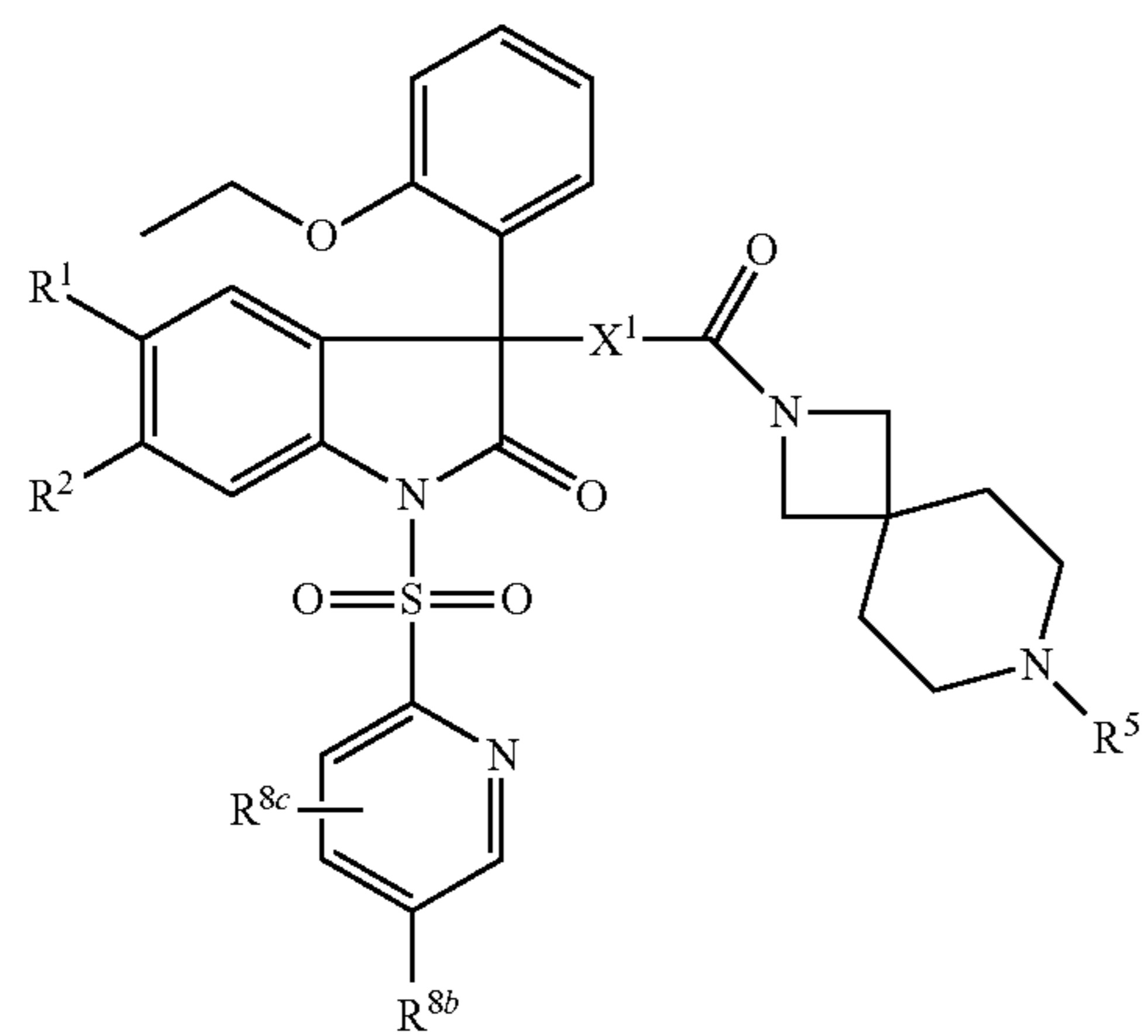
I.116



I.116

63

-continued



I.117

5

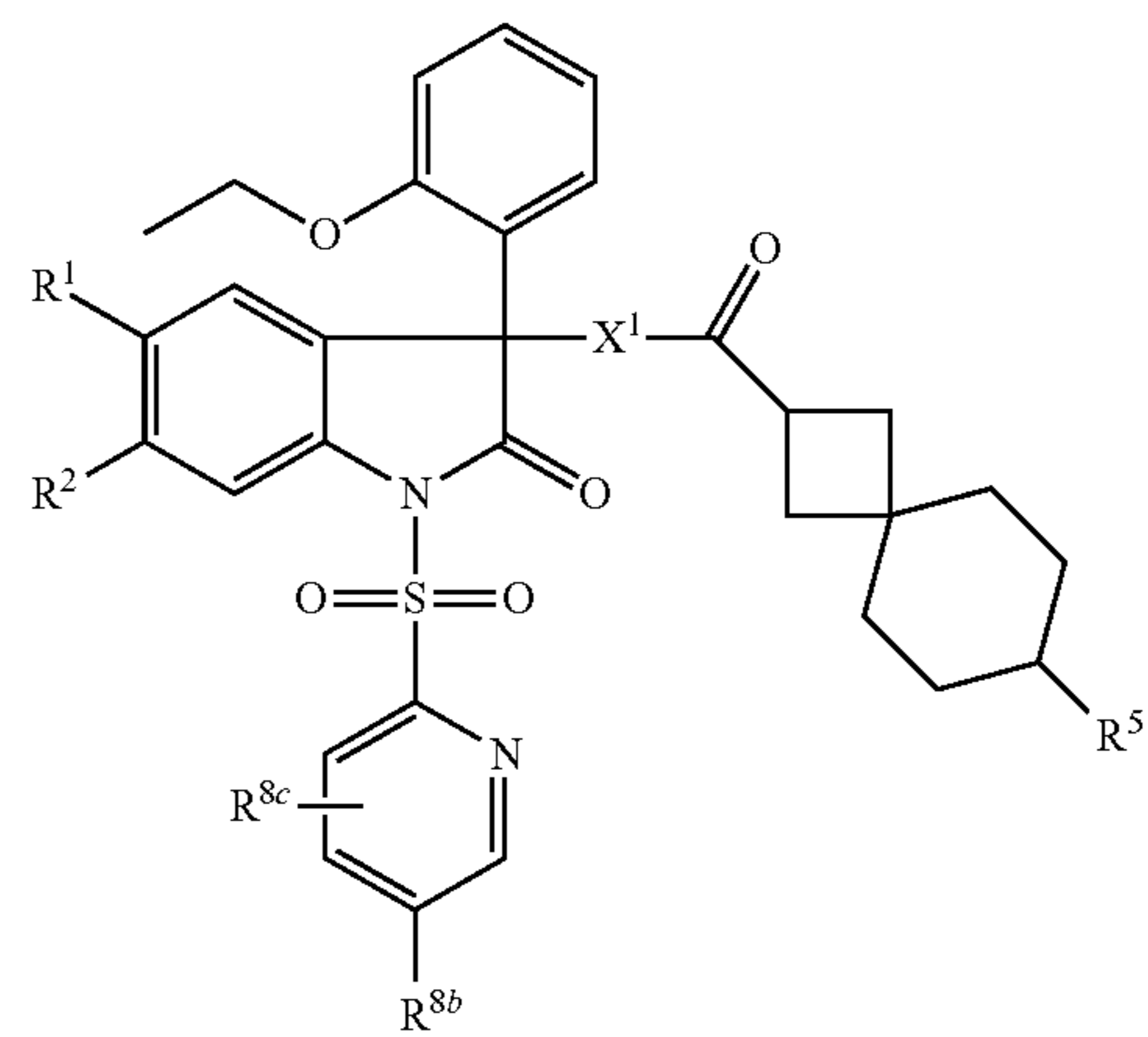
10

15

20

64

-continued



I.120

I.118

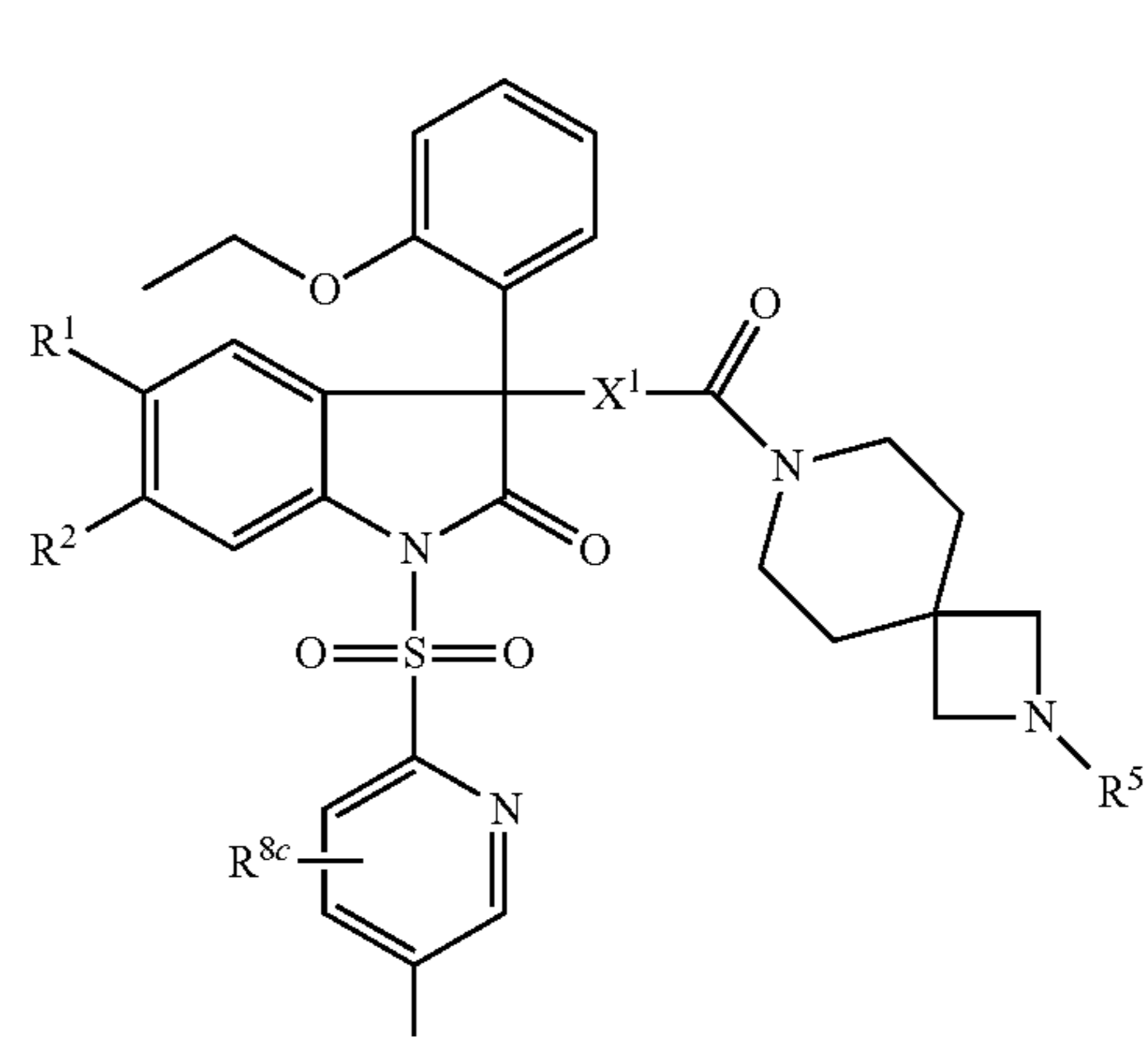
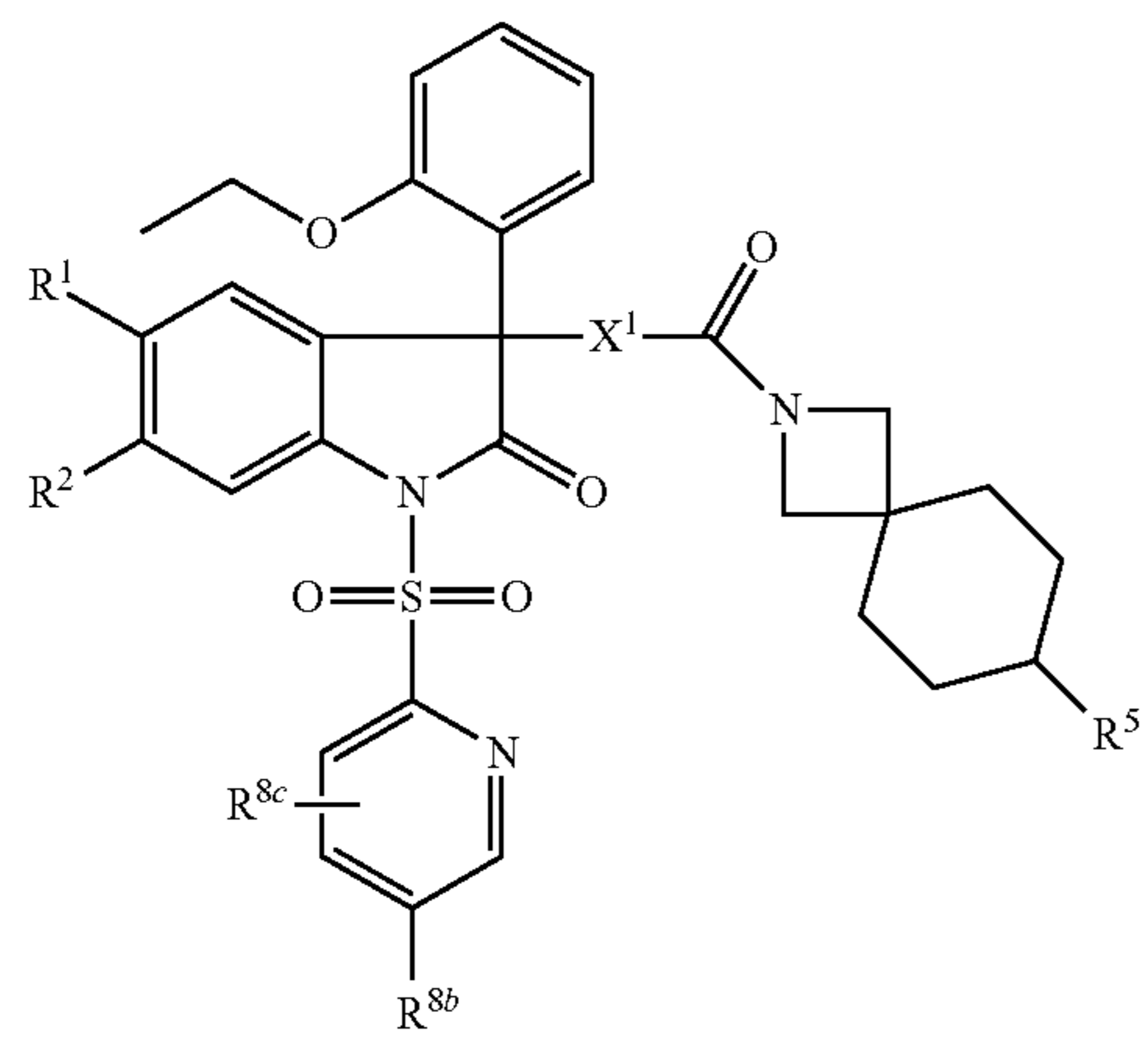
25

30

35

40

45



I.121

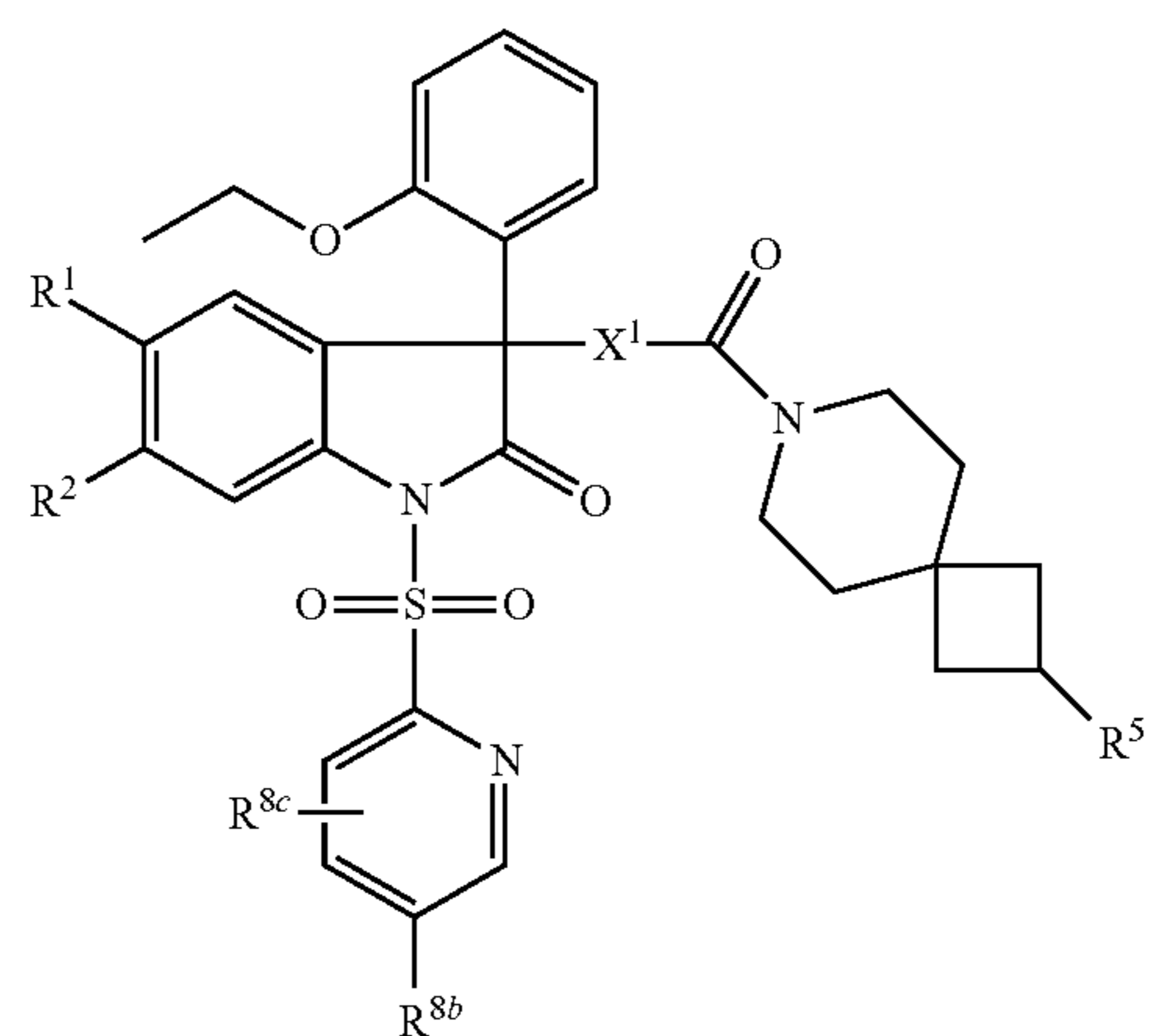
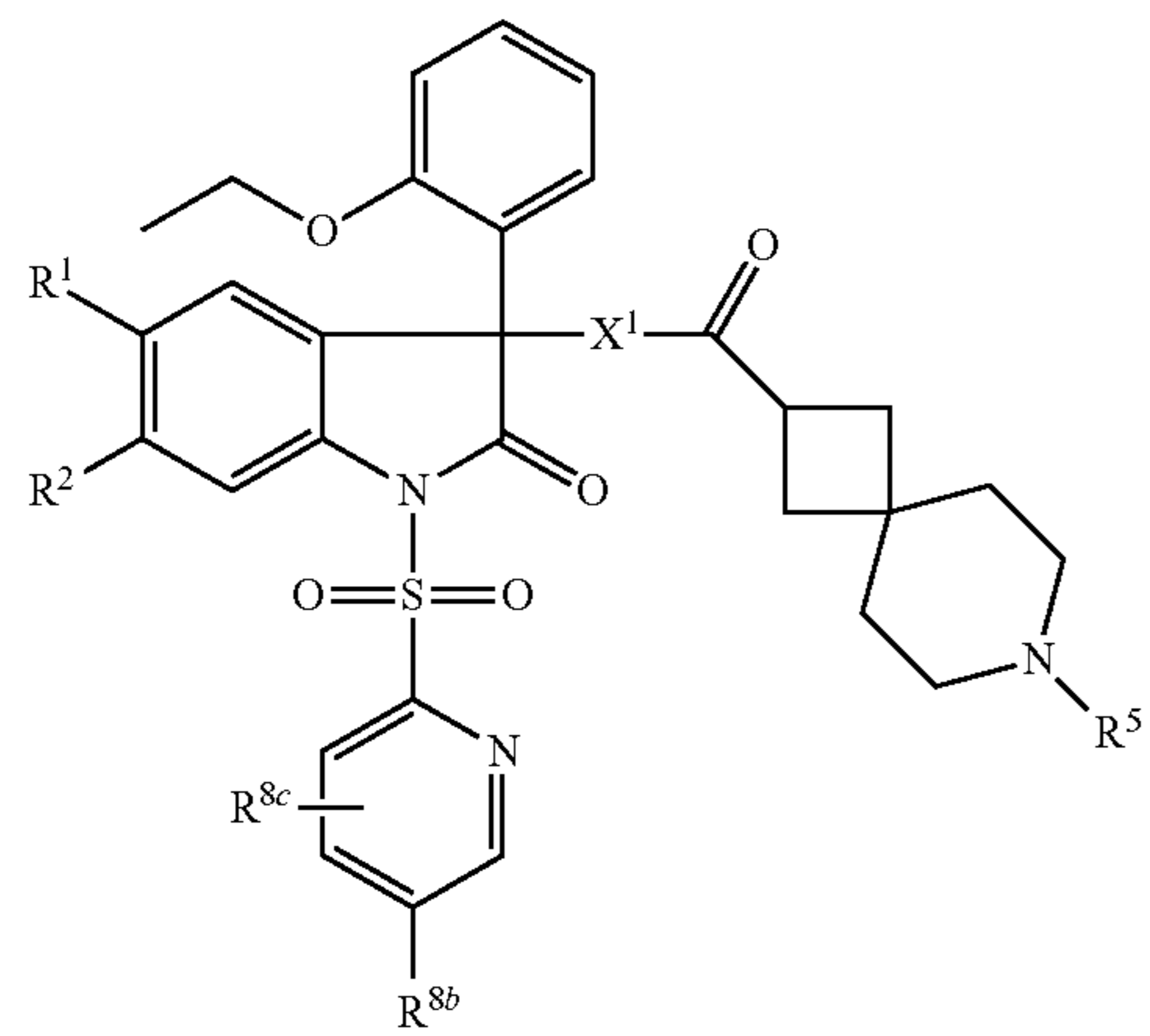
I.119

50

55

60

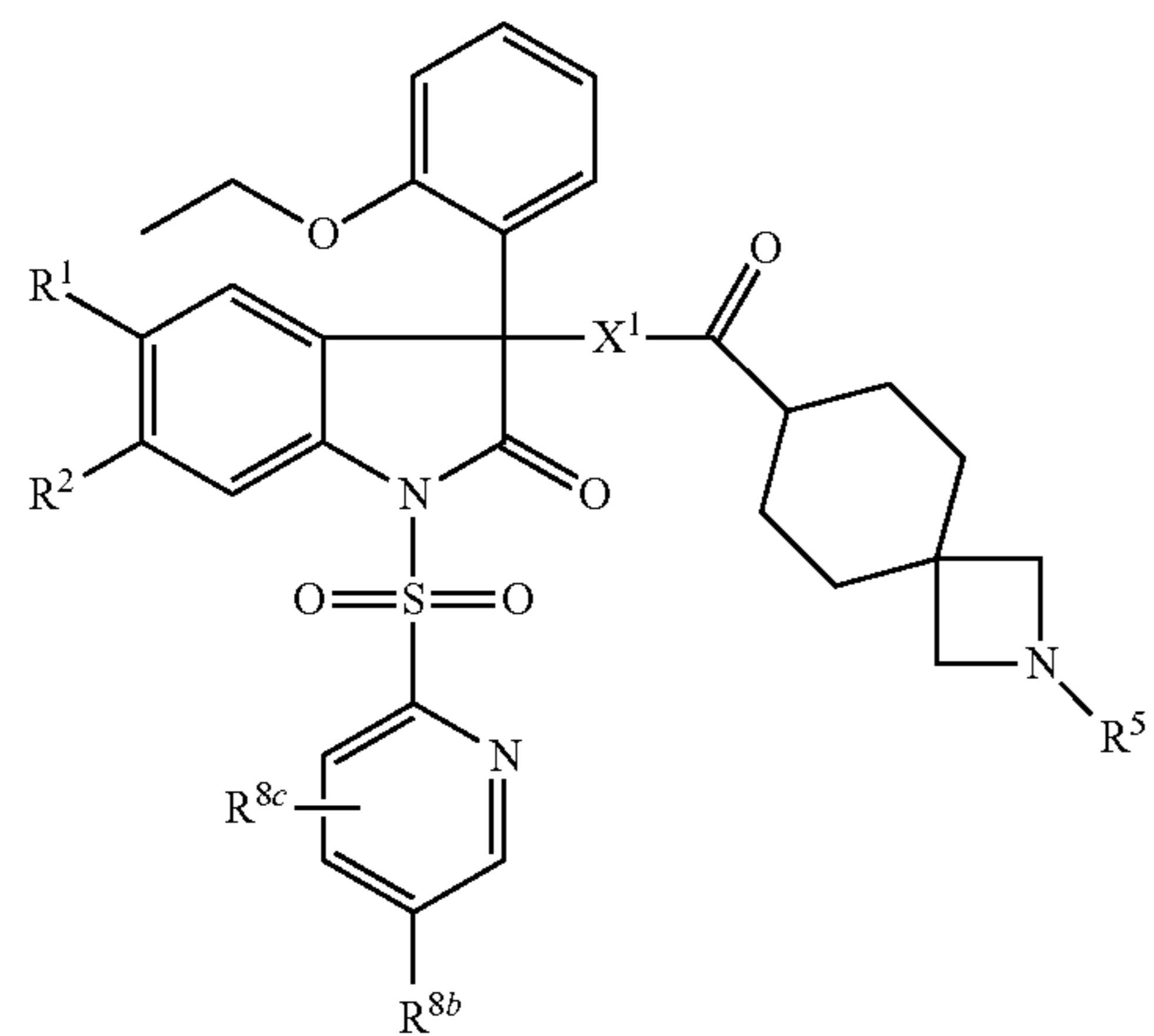
65



I.122

65

-continued



I.123

5

10

15

20

I.124

30

35

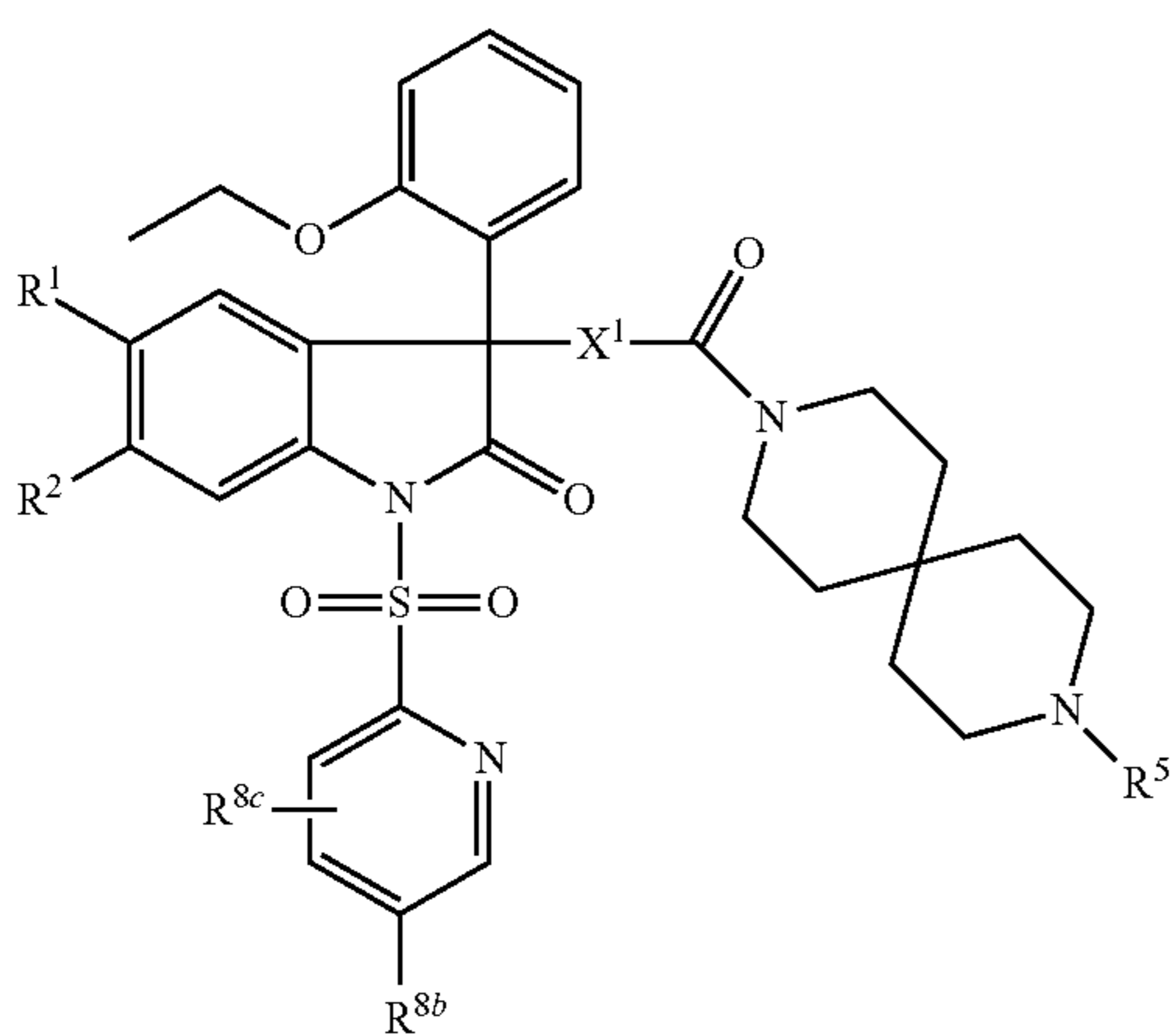
40

45

I.125

50

55

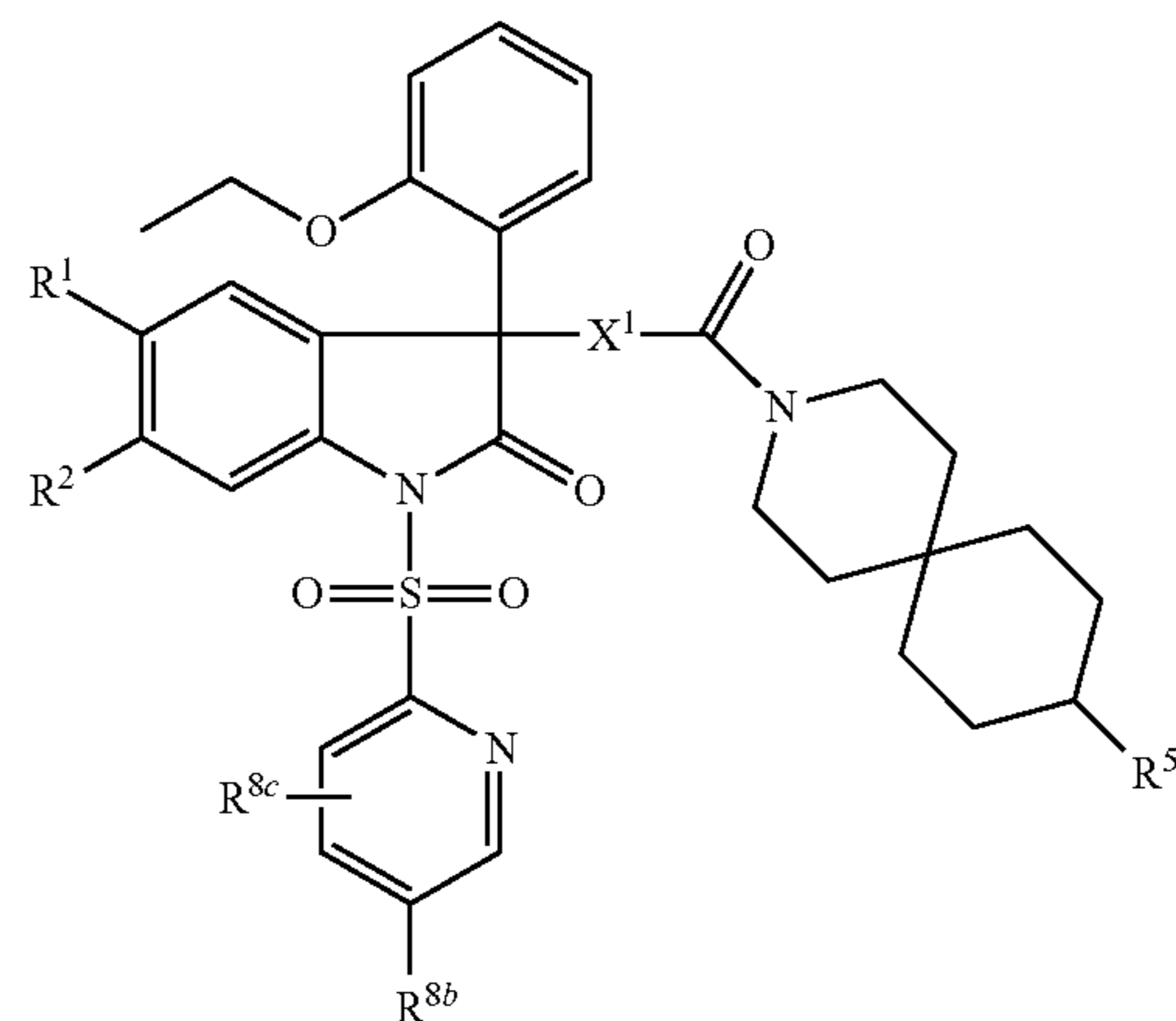


60

65

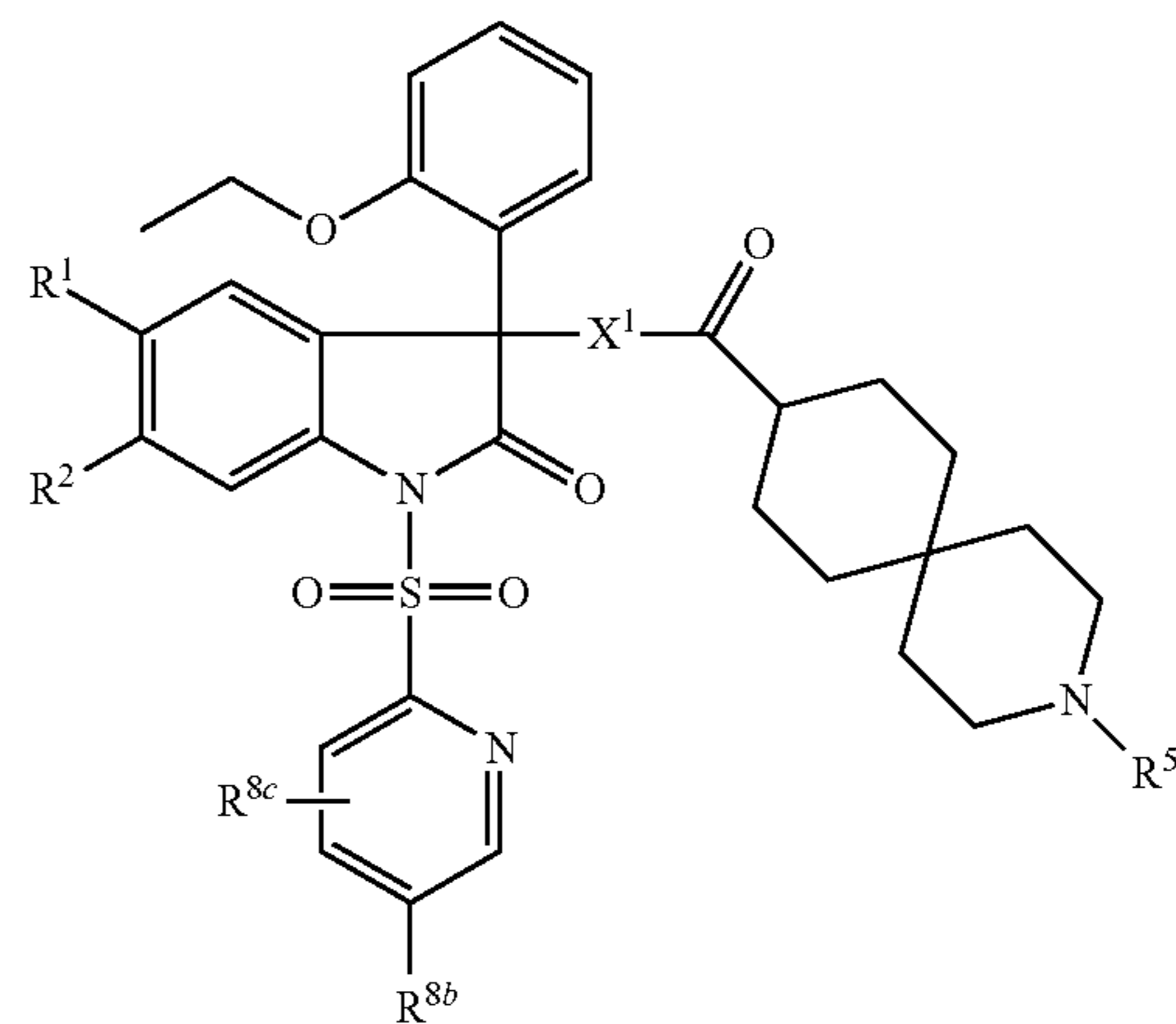
66

-continued



I.126

I.127



I.128

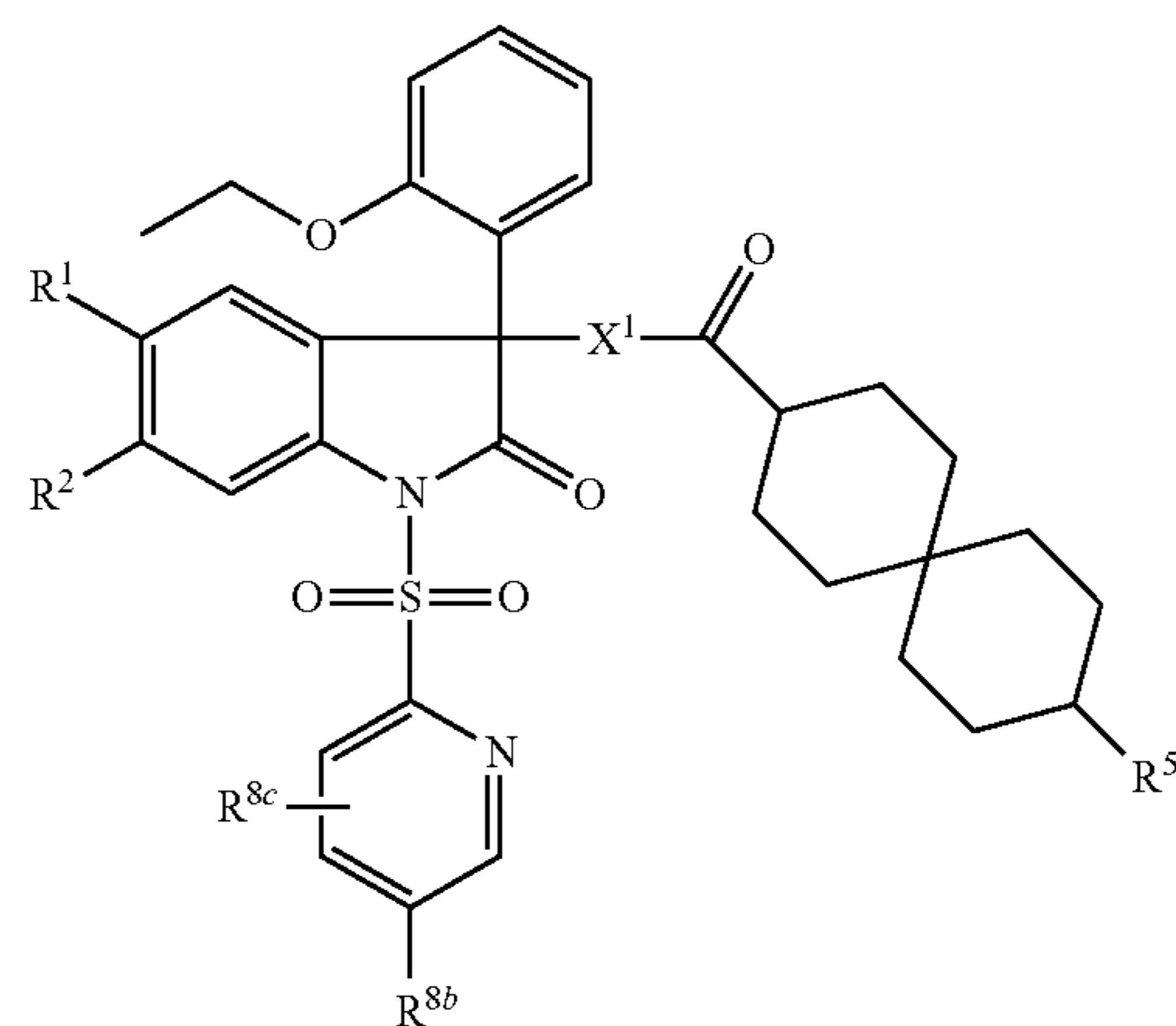


Table 1

Compounds of the formula I.1 in which X¹ is NH, R⁵ is hydrogen, and R¹, R², R^{8a}, R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table A

Table 2

Compounds of the formula I.1 in which X¹ is NH, R⁵ is methyl, and R¹, R², R^{8a}, R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table A

Table 3

Compounds of the formula I.1 in which X¹ is NH, R⁵ is ethyl, and R¹, R², R^{8a}, R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table A

Tables 51241 to 51540

Compounds of the formula I.123 in which X¹ and R⁵ are as defined in tables 1 to 300, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B Tables 51541 to 52080

Compounds of the formula I.124 in which X¹ and R⁵ are as defined in tables 301 to 840, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B Tables 52081 to 52380

Compounds of the formula I.125 in which X¹ and R⁵ are as defined in tables 1 to 300, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B Tables 52381 to 52920

Compounds of the formula I.126 in which X¹ and R⁵ are as defined in tables 301 to 840, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B Tables 52921 to 53220

Compounds of the formula I.127 in which X¹ and R⁵ are as defined in tables 1 to 300, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B Tables 53221 to 53760

Compounds of the formula I.128 in which X¹ and R⁵ are as defined in tables 301 to 840, and R¹, R², R^{8b} and R^{8c} for a compound corresponds in each case to one row of Table B

TABLE A

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-1.	H	H	H	CN	H
A-2.	F	H	H	CN	H
A-3.	CH ₃	H	H	CN	H
A-4.	OCH ₃	H	H	CN	H
A-5.	CH ₂ F	H	H	CN	H
A-6.	CHF ₂	H	H	CN	H
A-7.	CF ₃	H	H	CN	H
A-8.	OCH ₂ F	H	H	CN	H
A-9.	OCHF ₂	H	H	CN	H
A-10.	OCF ₃	H	H	CN	H
A-11.	H	F	H	CN	H
A-12.	H	CH ₃	H	CN	H
A-13.	H	OCH ₃	H	CN	H
A-14.	H	CN	H	CN	H
A-15.	H	CH ₂ F	H	CN	H
A-16.	H	CHF ₂	H	CN	H
A-17.	H	CF ₃	H	CN	H
A-18.	H	OCH ₂ F	H	CN	H
A-19.	H	OCHF ₂	H	CN	H
A-20.	H	OCF ₃	H	CN	H
A-21.	H	H	3-F	CN	H
A-22.	H	H	3-CH ₃	CN	H
A-23.	H	H	3-OCH ₃	CN	H
A-24.	H	H	5-F	CN	H
A-25.	H	H	5-CH ₃	CN	H
A-26.	H	H	5-OCH ₃	CN	H
A-27.	F	F	H	CN	H
A-28.	F	CH ₃	H	CN	H
A-29.	F	OCH ₃	H	CN	H
A-30.	F	CN	H	CN	H
A-31.	F	CH ₂ F	H	CN	H
A-32.	F	CHF ₂	H	CN	H
A-33.	F	CF ₃	H	CN	H
A-34.	F	OCH ₂ F	H	CN	H
A-35.	F	OCHF ₂	H	CN	H
A-36.	F	OCF ₃	H	CN	H
A-37.	F	H	3-F	CN	H
A-38.	F	H	3-CH ₃	CN	H
A-39.	F	H	3-OCH ₃	CN	H
A-40.	F	H	5-F	CN	H
A-41.	F	H	5-CH ₃	CN	H
A-42.	F	H	5-OCH ₃	CN	H
A-43.	CH ₃	F	H	CN	H
A-44.	CH ₃	CH ₃	H	CN	H
A-45.	CH ₃	OCH ₃	H	CN	H
A-46.	CH ₃	CN	H	CN	H
A-47.	CH ₃	CH ₂ F	H	CN	H

TABLE A-continued

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-48.	CH ₃	CHF ₂	H	CN	H
A-49.	CH ₃	CF ₃	H	CN	H
A-50.	CH ₃	OCH ₂ F	H	CN	H
A-51.	CH ₃	OCHF ₂	H	CN	H
A-52.	CH ₃	OCF ₃	H	CN	H
A-53.	CH ₃	H	3-F	CN	H
A-54.	CH ₃	H	3-CH ₃	CN	H
A-55.	CH ₃	H	3-OCH ₃	CN	H
A-56.	CH ₃	H	5-F	CN	H
A-57.	CH ₃	H	5-CH ₃	CN	H
A-58.	CH ₃	H	5-OCH ₃	CN	H
A-59.	OCH ₃	F	H	CN	H
A-60.	OCH ₃	CH ₃	H	CN	H
A-61.	OCH ₃	OCH ₃	H	CN	H
A-62.	OCH ₃	CN	H	CN	H
A-63.	OCH ₃	CH ₂ F	H	CN	H
A-64.	OCH ₃	CHF ₂	H	CN	H
A-65.	OCH ₃	CF ₃	H	CN	H
A-66.	OCH ₃	OCH ₂ F	H	CN	H
A-67.	OCH ₃	OCHF ₂	H	CN	H
A-68.	OCH ₃	OCF ₃	H	CN	H
A-69.	OCH ₃	H	3-F	CN	H
A-70.	OCH ₃	H	3-CH ₃	CN	H
A-71.	OCH ₃	H	3-OCH ₃	CN	H
A-72.	OCH ₃	H	5-F	CN	H
A-73.	OCH ₃	H	5-CH ₃	CN	H
A-74.	OCH ₃	H	5-OCH ₃	CN	H
A-75.	H	F	3-F	CN	H
A-76.	H	F	3-CH ₃	CN	H
A-77.	H	F	3-OCH ₃	CN	H
A-78.	H	F	5-F	CN	H
A-79.	H	F	5-CH ₃	CN	H
A-80.	H	F	5-OCH ₃	CN	H
A-81.	H	CH ₃	3-F	CN	H
A-82.	H	CH ₃	3-CH ₃	CN	H
A-83.	H	CH ₃	3-OCH ₃	CN	H
A-84.	H	CH ₃	5-F	CN	H
A-85.	H	CH ₃	5-CH ₃	CN	H
A-86.	H	CH ₃	5-OCH ₃	CN	H
A-87.	H	OCH ₃	3-F	CN	H
A-88.	H	OCH ₃	3-CH ₃	CN	H
A-89.	H	OCH ₃	3-OCH ₃	CN	H
A-90.	H	OCH ₃	5-F	CN	H
A-91.	H	OCH ₃	5-CH ₃	CN	H
A-92.	H	OCH ₃	5-OCH ₃	CN	H
A-93.	H	CN	3-F	CN	H
A-94.	H	CN	3-CH ₃	CN	H
A-95.	H	CN	3-OCH ₃	CN	H
A-96.	H	CN	5-F	CN	H
A-97.	H	CN	5-CH ₃	CN	H
A-98.	H	CN	5-OCH ₃	CN	H
A-99.	H	CH ₂ F	3-F	CN	H
A-100.	H	CH ₂ F	3-CH ₃	CN	H
A-101.	H	CH ₂ F	3-OCH ₃	CN	H
A-102.	H	CH ₂ F	5-F	CN	H
A-103.	H	CH ₂ F	5-CH ₃	CN	H
A-104.	H	CH ₂ F	5-OCH ₃	CN	H
A-105.	H	CHF ₂	3-F	CN	H
A-106.	H	CHF ₂	3-CH ₃	CN	H
A-107.	H	CHF ₂	3-OCH ₃	CN	H
A-108.	H	CHF ₂	5-F	CN	H
A-109.	H	CHF ₂	5-CH ₃	CN	H
A-110.	H	CHF ₂	5-OCH ₃	CN	H
A-111.	H	CF ₃	3-F	CN	H
A-112.	H	CF ₃	3-CH ₃	CN	H
A-113.	H	CF ₃	3-OCH ₃	CN	H
A-114.	H	CF ₃	5-F	CN	H
A-115.	H	CF ₃	5-CH ₃	CN	H
A-116.	H	CF ₃	5-OCH ₃	CN	H
A-117.	H	OCH ₂ F	3-F	CN	H
A-118.	H	OCH ₂ F	3-CH ₃	CN	H
A-119.	H	OCH ₂ F	3-OCH ₃	CN	H
A-120.	H	OCH ₂ F	5-F	CN	H
A-121.	H	OCH ₂ F	5-CH ₃	CN	H
A-122.	H	OCH ₂ F	5-OCH ₃	CN	H
A-123.	H	OCHF ₂	3-F	CN	H
A-124.	H	OCHF ₂	3-CH ₃	CN	H
A-125.	H	OCHF ₂	3-OCH ₃	CN	H

TABLE A-continued

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-750.	H	F	3-CH ₃	F	H
A-751.	H	F	3-OCH ₃	F	H
A-752.	H	F	5-F	F	H
A-753.	H	F	5-CH ₃	F	H
A-754.	H	F	5-OCH ₃	F	H
A-755.	H	CH ₃	3-F	F	H
A-756.	H	CH ₃	3-CH ₃	F	H
A-757.	H	CH ₃	3-OCH ₃	F	H
A-758.	H	CH ₃	5-F	F	H
A-759.	H	CH ₃	5-CH ₃	F	H
A-760.	H	CH ₃	5-OCH ₃	F	H
A-761.	H	OCH ₃	3-F	F	H
A-762.	H	OCH ₃	3-CH ₃	F	H
A-763.	H	OCH ₃	3-OCH ₃	F	H
A-764.	H	OCH ₃	5-F	F	H
A-765.	H	OCH ₃	5-CH ₃	F	H
A-766.	H	OCH ₃	5-OCH ₃	F	H
A-767.	H	CN	3-F	F	H
A-768.	H	CN	3-CH ₃	F	H
A-769.	H	CN	3-OCH ₃	F	H
A-770.	H	CN	5-F	F	H
A-771.	H	CN	5-CH ₃	F	H
A-772.	H	CN	5-OCH ₃	F	H
A-773.	H	CH ₂ F	3-F	F	H
A-774.	H	CH ₂ F	3-CH ₃	F	H
A-775.	H	CH ₂ F	3-OCH ₃	F	H
A-776.	H	CH ₂ F	5-F	F	H
A-777.	H	CH ₂ F	5-CH ₃	F	H
A-778.	H	CH ₂ F	5-OCH ₃	F	H
A-779.	H	CHF ₂	3-F	F	H
A-780.	H	CHF ₂	3-CH ₃	F	H
A-781.	H	CHF ₂	3-OCH ₃	F	H
A-782.	H	CHF ₂	5-F	F	H
A-783.	H	CHF ₂	5-CH ₃	F	H
A-784.	H	CHF ₂	5-OCH ₃	F	H
A-785.	H	CF ₃	3-F	F	H
A-786.	H	CF ₃	3-CH ₃	F	H
A-787.	H	CF ₃	3-OCH ₃	F	H
A-788.	H	CF ₃	5-F	F	H
A-789.	H	CF ₃	5-CH ₃	F	H
A-790.	H	CF ₃	5-OCH ₃	F	H
A-791.	H	OCH ₂ F	3-F	F	H
A-792.	H	OCH ₂ F	3-CH ₃	F	H
A-793.	H	OCH ₂ F	3-OCH ₃	F	H
A-794.	H	OCH ₂ F	5-F	F	H
A-795.	H	OCH ₂ F	5-CH ₃	F	H
A-796.	H	OCH ₂ F	5-OCH ₃	F	H
A-797.	H	OCHF ₂	3-F	F	H
A-798.	H	OCHF ₂	3-CH ₃	F	H
A-799.	H	OCHF ₂	3-OCH ₃	F	H
A-800.	H	OCHF ₂	5-F	F	H
A-801.	H	OCHF ₂	5-CH ₃	F	H
A-802.	H	OCHF ₂	5-OCH ₃	F	H
A-803.	H	OCF ₃	3-F	F	H
A-804.	H	OCF ₃	3-CH ₃	F	H
A-805.	H	OCF ₃	3-OCH ₃	F	H
A-806.	H	OCF ₃	5-F	F	H
A-807.	H	OCF ₃	5-CH ₃	F	H
A-808.	H	OCF ₃	5-OCH ₃	F	H
A-809.	F	F	3-F	F	H
A-810.	F	F	3-CH ₃	F	H
A-811.	F	F	3-OCH ₃	F	H
A-812.	F	F	5-F	F	H
A-813.	F	F	5-CH ₃	F	H
A-814.	F	F	5-OCH ₃	F	H
A-815.	F	CH ₃	3-F	F	H
A-816.	F	CH ₃	3-CH ₃	F	H
A-817.	F	CH ₃	3-OCH ₃	F	H
A-818.	F	CH ₃	5-F	F	H
A-819.	F	CH ₃	5-CH ₃	F	H
A-820.	F	CH ₃	5-OCH ₃	F	H
A-821.	F	OCH ₃	3-F	F	H
A-822.	F	OCH ₃	3-CH ₃	F	H
A-823.	F	OCH ₃	3-OCH ₃	F	H
A-824.	F	OCH ₃	5-F	F	H
A-825.	F	OCH ₃	5-CH ₃	F	H
A-826.	F	OCH ₃	5-OCH ₃	F	H
A-827.	F	CN	3-F	F	H

TABLE A-continued

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-828.	F	CN	3-CH ₃	F	H
A-829.	F	CN	3-OCH ₃	F	H
A-830.	F	CN	5-F	F	H
A-831.	F	CN	5-CH ₃	F	H
A-832.	F	CN	5-OCH ₃	F	H
A-833.	F	CH ₂ F	3-F	F	H
A-834.	F	CH ₂ F	3-CH ₃	F	H
A-835.	F	CH ₂ F	3-OCH ₃	F	H
A-836.	F	CH ₂ F	5-F	F	H
A-837.	F	CH ₂ F	5-CH ₃	F	H
A-838.	F	CH ₂ F	5-OCH ₃	F	H
A-839.	F	CHF ₂	3-F	F	H
A-840.	F	CHF ₂	3-CH ₃	F	H
A-841.	F	CHF ₂	3-OCH ₃	F	H
A-842.	F	CHF ₂	5-F	F	H
A-843.	F	CHF ₂	5-CH ₃	F	H
A-844.	F	CHF ₂	5-OCH ₃	F	H
A-845.	F	CF ₃	3-F	F	H
A-846.	F	CF ₃	3-CH ₃	F	H
A-847.	F	CF ₃	3-OCH ₃	F	H
A-848.	F	CF ₃	5-F	F	H
A-849.	F	CF ₃	5-CH ₃	F	H
A-850.	F	CF ₃	5-OCH ₃	F	H
A-851.	F	OCH ₂ F	3-F	F	H
A-852.	F	OCH ₂ F	3-CH ₃	F	H
A-853.	F	OCH ₂ F	3-OCH ₃	F	H
A-854.	F	OCH ₂ F	5-F	F	H
A-855.	F	OCH ₂ F	5-CH ₃	F	H
A-856.	F	OCH ₂ F	5-OCH ₃	F	H
A-857.	F	OCHF ₂	3-F	F	H
A-858.	F	OCHF ₂	3-CH ₃	F	H
A-859.	F	OCHF ₂	3-OCH ₃	F	H
A-860.	F	OCHF ₂	5-F	F	H
A-861.	F	OCHF ₂	5-CH ₃	F	H
A-862.	F	OCHF ₂	5-OCH ₃	F	H
A-863.	F	OCF ₃	3-F	F	H
A-864.	F	OCF ₃	3-CH ₃	F	H
A-865.	F	OCF ₃	3-OCH ₃	F	H
A-866.	F	OCF ₃	5-F	F	H
A-867.	F	OCF ₃	5-CH ₃	F	H
A-868.	F	OCF ₃	5-OCH ₃	F	H
A-869.	CH ₃	F	3-F	F	H
A-870.	CH ₃	F	3-CH ₃	F	H
A-871.	CH ₃	F	3-OCH ₃	F	H
A-872.	CH ₃	F	5-F	F	H
A-873.	CH ₃	F	5-CH ₃	F	H
A-874.	CH ₃	F	5-OCH ₃	F	H
A-875.	CH ₃	CH ₃	3-F	F	H
A-876.	CH ₃	CH ₃	3-CH ₃	F	H
A-877.	CH ₃	CH ₃	3-OCH ₃	F	H
A-878.	CH ₃	CH ₃	5-F	F	H
A-879.	CH ₃	CH ₃	5-CH ₃	F	H
A-880.	CH ₃	CH ₃	5-OCH ₃	F	H
A-881.	CH ₃	OCH ₃	3-F	F	H
A-882.	CH ₃	OCH ₃	3-CH ₃	F	H
A-883.	CH ₃	OCH ₃	3-OCH ₃	F	H
A-884.	CH ₃	OCH ₃	5-F	F	H
A-885.	CH ₃	OCH ₃	5-CH ₃	F	H
A-886.	CH ₃	OCH ₃	5-OCH ₃	F	H
A-887.	CH ₃	CN	3-F	F	H
A-888.	CH ₃	CN	3-CH ₃	F	H
A-889.	CH ₃	CN	3-OCH ₃	F	H
A-890.	CH ₃	CN	5-F	F	H
A-891.	CH ₃	CN	5-CH ₃	F	H
A-892.	CH ₃	CN	5-OCH ₃	F	H
A-893.	CH ₃	CH ₂ F	3-F	F	H
A-894.	CH ₃	CH ₂ F	3-CH ₃	F	H
A-895.	CH ₃	CH ₂ F	3-OCH ₃	F	H
A-896.	CH ₃	CH ₂ F	5-F	F	H
A-897.	CH ₃	CH ₂ F	5-CH ₃	F	H
A-898.	CH ₃	CH ₂ F	5-OCH ₃	F	H
A-899.	CH ₃	CHF ₂	3-F	F	H
A-900.	CH ₃	CHF ₂	3-CH ₃	F	H
A-901.	CH ₃	CHF ₂	3-OCH ₃	F	H
A-902.	CH ₃	CHF ₂	5-F	F	H
A-903.	CH ₃	CHF ₂	5-CH ₃	F	H
A-904.	CH ₃	CHF ₂	5-OCH ₃	F	H
A-905.	CH ₃	CF ₃	3-F	F	H

TABLE A-continued

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-1374.	H	H	5-OCH ₃	Cl	H
A-1375.	F	F	H	Cl	H
A-1376.	F	CH ₃	H	Cl	H
A-1377.	F	OCH ₃	H	Cl	H
A-1378.	F	CN	H	Cl	H
A-1379.	F	CH ₂ F	H	Cl	H
A-1380.	F	CHF ₂	H	Cl	H
A-1381.	F	CF ₃	H	Cl	H
A-1382.	F	OCH ₂ F	H	Cl	H
A-1383.	F	OCHF ₂	H	Cl	H
A-1384.	F	OCF ₃	H	Cl	H
A-1385.	F	H	3-F	Cl	H
A-1386.	F	H	3-CH ₃	Cl	H
A-1387.	F	H	3-OCH ₃	Cl	H
A-1388.	F	H	5-F	Cl	H
A-1389.	F	H	5-CH ₃	Cl	H
A-1390.	F	H	5-OCH ₃	Cl	H
A-1391.	CH ₃	F	H	Cl	H
A-1392.	CH ₃	CH ₃	H	Cl	H
A-1393.	CH ₃	OCH ₃	H	Cl	H
A-1394.	CH ₃	CN	H	Cl	H
A-1395.	CH ₃	CH ₂ F	H	Cl	H
A-1396.	CH ₃	CHF ₂	H	Cl	H
A-1397.	CH ₃	CF ₃	H	Cl	H
A-1398.	CH ₃	OCH ₂ F	H	Cl	H
A-1399.	CH ₃	OCHF ₂	H	Cl	H
A-1400.	CH ₃	OCF ₃	H	Cl	H
A-1401.	CH ₃	H	3-F	Cl	H
A-1402.	CH ₃	H	3-CH ₃	Cl	H
A-1403.	CH ₃	H	3-OCH ₃	Cl	H
A-1404.	CH ₃	H	5-F	Cl	H
A-1405.	CH ₃	H	5-CH ₃	Cl	H
A-1406.	CH ₃	H	5-OCH ₃	Cl	H
A-1407.	OCH ₃	F	H	Cl	H
A-1408.	OCH ₃	CH ₃	H	Cl	H
A-1409.	OCH ₃	OCH ₃	H	Cl	H
A-1410.	OCH ₃	CN	H	Cl	H
A-1411.	OCH ₃	CH ₂ F	H	Cl	H
A-1412.	OCH ₃	CHF ₂	H	Cl	H
A-1413.	OCH ₃	CF ₃	H	Cl	H
A-1414.	OCH ₃	OCH ₂ F	H	Cl	H
A-1415.	OCH ₃	OCHF ₂	H	Cl	H
A-1416.	OCH ₃	OCF ₃	H	Cl	H
A-1417.	OCH ₃	H	3-F	Cl	H
A-1418.	OCH ₃	H	3-CH ₃	Cl	H
A-1419.	OCH ₃	H	3-OCH ₃	Cl	H
A-1420.	OCH ₃	H	5-F	Cl	H
A-1421.	OCH ₃	H	5-CH ₃	Cl	H
A-1422.	OCH ₃	H	5-OCH ₃	Cl	H
A-1423.	H	F	3-F	Cl	H
A-1424.	H	F	3-CH ₃	Cl	H
A-1425.	H	F	3-OCH ₃	Cl	H
A-1426.	H	F	5-F	Cl	H
A-1427.	H	F	5-CH ₃	Cl	H
A-1428.	H	F	5-OCH ₃	Cl	H
A-1429.	H	CH ₃	3-F	Cl	H
A-1430.	H	CH ₃	3-CH ₃	Cl	H
A-1431.	H	CH ₃	3-OCH ₃	Cl	H
A-1432.	H	CH ₃	5-F	Cl	H
A-1433.	H	CH ₃	5-CH ₃	Cl	H
A-1434.	H	CH ₃	5-OCH ₃	Cl	H
A-1435.	H	OCH ₃	3-F	Cl	H
A-1436.	H	OCH ₃	3-CH ₃	Cl	H
A-1437.	H	OCH ₃	3-OCH ₃	Cl	H
A-1438.	H	OCH ₃	5-F	Cl	H
A-1439.	H	OCH ₃	5-CH ₃	Cl	H
A-1440.	H	OCH ₃	5-OCH ₃	Cl	H
A-1441.	H	CN	3-F	Cl	H
A-1442.	H	CN	3-CH ₃	Cl	H
A-1443.	H	CN	3-OCH ₃	Cl	H
A-1444.	H	CN	5-F	Cl	H
A-1445.	H	CN	5-CH ₃	Cl	H
A-1446.	H	CN	5-OCH ₃	Cl	H
A-1447.	H	CH ₂ F	3-F	Cl	H
A-1448.	H	CH ₂ F	3-CH ₃	Cl	H
A-1449.	H	CH ₂ F	3-OCH ₃	Cl	H
A-1450.	H	CH ₂ F	5-F	Cl	H
A-1451.	H	CH ₂ F	5-CH ₃	Cl	H

TABLE A-continued

Example No.	R ^{8a}	R ^{8b}	R ^{8c}	R ¹	R ²
A-1452.	H	CH ₂ F	5-OCH ₃	Cl	H
A-1453.	H	CHF ₂	3-F	Cl	H
A-1454.	H	CHF ₂	3-CH ₃	Cl	H
A-1455.	H	CHF ₂	3-OCH ₃	Cl	H
A-1456.	H	CHF ₂	5-F	Cl	H
A-1457.	H	CHF ₂	5-CH ₃	Cl	H
A-1458.	H	CHF ₂	5-OCH ₃	Cl	H
A-1459.	H	CF ₃	3-F	Cl	H
A-1460.	H	CF ₃	3-CH ₃	Cl	H
A-1461.	H	CF ₃	3-OCH ₃	Cl	H
A-1462.	H	CF ₃	5-F	Cl	H
A-1463.	H	CF ₃	5-CH ₃	Cl	H
A-1464.	H	CF ₃	5-OCH ₃	Cl	H
A-1465.	H	OCH ₂ F	3-F	Cl	H
A-1466.	H	OCH ₂ F	3-CH ₃	Cl	H
A-1467.	H	OCH ₂ F	3-OCH ₃	Cl	H
A-1468.	H	OCH ₂ F	5-F	Cl	H
A-1469.	H	OCH ₂ F	5-CH ₃	Cl	H
A-1470.	H	OCH ₂ F	5-OCH ₃	Cl	H
A-1471.	H	OCHF ₂	3-F	Cl	H
A-1472.	H	OCHF ₂	3-CH ₃	Cl	H
A-1473.	H	OCHF ₂	3-OCH ₃	Cl	H
A-1474.	H	OCHF ₂	5-F	Cl	H
A-1475.	H	OCHF ₂	5-CH ₃	Cl	H
A-1476.	H	OCHF ₂	5-OCH ₃	Cl	H
A-1477.	H	OCF ₃	3-F	Cl	H
A-1478.	H	OCF ₃	3-CH ₃	Cl	H
A-1479.	H	OCF ₃	3-OCH ₃	Cl	H
A-1480.	H	OCF ₃	5-F	Cl	H
A-1481.	H	OCF ₃	5-CH ₃	Cl	H
A-1482.	H	OCF ₃	5-OCH ₃	Cl	H
A-1483.	F	F	3-F	Cl	H
A-1484.	F	F	3-CH ₃	Cl	H
A-1485.	F	F	3-OCH ₃	Cl	H
A-1486.	F	F	5-F	Cl	H
A-1487.	F	F	5-CH ₃	Cl	H
A-1488.	F	F	5-OCH ₃	Cl	H
A-1489.	F	CH ₃	3-F	Cl	H
A-1490.	F	CH ₃	3-CH ₃	Cl	H
A-1491.	F	CH ₃	3-OCH ₃	Cl	H
A-1492.	F	CH ₃	5-F	Cl	H
A-1493.	F	CH ₃	5-CH ₃	Cl	H
A-1494.	F	CH ₃	5-OCH ₃	Cl	H
A-1495.	F	OCH ₃	3-F	Cl	H
A-1496.	F	OCH ₃	3-CH ₃	Cl	H
A-1497.	F	OCH ₃	3-OCH ₃	Cl	H
A-1498.	F	OCH ₃	5-F	Cl	H
A-1499.	F	OCH ₃	5-CH ₃	Cl	H
A-1500.	F	OCH ₃	5-OCH ₃	Cl	H
A-1501.	F	CN	3-F	Cl	H
A-1502.	F	CN	3-CH ₃	Cl	H
A-1503.	F	CN	3-OCH ₃	Cl	H
A-1504.	F	CN	5-F	Cl	H
A-1505.	F	CN	5-CH ₃	Cl	H
A-1506.	F	CN	5-OCH ₃	Cl	H
A-1507.	F	CH ₂ F	3-F	Cl	H
A-1508.	F	CH ₂ F	3-CH ₃	Cl	H
A-1509.	F	CH ₂ F	3-OCH ₃	Cl	H
A-1510.	F	CH ₂ F	5-F	Cl	H
A-1511.	F	CH ₂ F	5-CH ₃	Cl	H
A-1512.	F	CH ₂ F	5-OCH ₃	Cl	H
A-1513.	F	CHF ₂	3-F	Cl	H
A-1514.	F	CHF ₂	3-CH ₃	Cl	H
A-1515.	F	CHF ₂	3-OCH ₃	Cl	H
A-1516.	F	CHF ₂	5-F	Cl	H
A-1517.	F	CHF ₂	5-CH ₃	Cl	H
A-1518.	F	CHF ₂	5-OCH ₃	Cl	H
A-2807.	H	CF ₃	3-F	F	F
A-2808.	H	CF ₃	3-CH ₃	F	F
A-2809.	H	CF ₃	3-OCH ₃	F	F
A-2810.	H	CF ₃	5-F	F	F
A-2811.	H	CF ₃	5-CH ₃	F	F
A-2812.	H	CF ₃	5-OCH ₃	F	F
A-2813.	H	OCH ₂ F	3-F	F	F
A-2814.	H	OCH ₂ F	3-CH ₃	F	F
A-2815.	H	OCH ₂ F	3-OCH ₃	F	F
A-2816.	H	OCH ₂ F	5-F	F	F
A-2817.	H	OCH ₂ F	5-CH ₃	F	F

123

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-14.	H	3-OCH ₃	CN	H
B-15.	H	5-F	CN	H
B-16.	H	5-CH ₃	CN	H
B-17.	H	5-OCH ₃	CN	H
B-18.	H	6-F	CN	H
B-19.	H	6-CH ₃	CN	H
B-20.	H	6-OCH ₃	CN	H
B-21.	F	3-F	CN	H
B-22.	F	3-CH ₃	CN	H
B-23.	F	3-OCH ₃	CN	H
B-24.	F	5-F	CN	H
B-25.	F	5-CH ₃	CN	H
B-26.	F	5-OCH ₃	CN	H
B-27.	F	6-F	CN	H
B-28.	F	6-CH ₃	CN	H
B-29.	F	6-OCH ₃	CN	H
B-30.	CH ₃	3-F	CN	H
B-31.	CH ₃	3-CH ₃	CN	H
B-32.	CH ₃	3-OCH ₃	CN	H
B-33.	CH ₃	5-F	CN	H
B-34.	CH ₃	5-CH ₃	CN	H
B-35.	CH ₃	5-OCH ₃	CN	H
B-36.	CH ₃	6-F	CN	H
B-37.	CH ₃	6-CH ₃	CN	H
B-38.	CH ₃	6-OCH ₃	CN	H
B-39.	OCH ₃	3-F	CN	H
B-40.	OCH ₃	3-CH ₃	CN	H
B-41.	OCH ₃	3-OCH ₃	CN	H
B-42.	OCH ₃	5-F	CN	H
B-43.	OCH ₃	5-CH ₃	CN	H
B-44.	OCH ₃	5-OCH ₃	CN	H
B-45.	OCH ₃	6-F	CN	H
B-46.	OCH ₃	6-CH ₃	CN	H
B-47.	OCH ₃	6-OCH ₃	CN	H
B-48.	CN	3-F	CN	H
B-49.	CN	3-CH ₃	CN	H
B-50.	CN	3-OCH ₃	CN	H
B-51.	CN	5-F	CN	H
B-52.	CN	5-CH ₃	CN	H
B-53.	CN	5-OCH ₃	CN	H
B-54.	CN	6-F	CN	H
B-55.	CN	6-CH ₃	CN	H
B-56.	CN	6-OCH ₃	CN	H
B-57.	CH ₂ F	3-F	CN	H
B-58.	CH ₂ F	3-CH ₃	CN	H
B-59.	CH ₂ F	3-OCH ₃	CN	H
B-60.	CH ₂ F	5-F	CN	H
B-61.	CH ₂ F	5-CH ₃	CN	H
B-62.	CH ₂ F	5-OCH ₃	CN	H
B-63.	CH ₂ F	6-F	CN	H
B-64.	CH ₂ F	6-CH ₃	CN	H
B-65.	CH ₂ F	6-OCH ₃	CN	H
B-66.	CHF ₂	3-F	CN	H
B-67.	CHF ₂	3-CH ₃	CN	H
B-68.	CHF ₂	3-OCH ₃	CN	H
B-69.	CHF ₂	5-F	CN	H
B-70.	CHF ₂	5-CH ₃	CN	H
B-71.	CHF ₂	5-OCH ₃	CN	H
B-72.	CHF ₂	6-F	CN	H
B-73.	CHF ₂	6-CH ₃	CN	H
B-74.	CHF ₂	6-OCH ₃	CN	H
B-75.	CF ₃	3-F	CN	H
B-76.	CF ₃	3-CH ₃	CN	H
B-77.	CF ₃	3-OCH ₃	CN	H
B-78.	CF ₃	5-F	CN	H
B-79.	CF ₃	5-CH ₃	CN	H
B-80.	CF ₃	5-OCH ₃	CN	H
B-81.	CF ₃	6-F	CN	H
B-82.	CF ₃	6-CH ₃	CN	H
B-83.	CF ₃	6-OCH ₃	CN	H
B-84.	OCH ₂ F	3-F	CN	H
B-85.	OCH ₂ F	3-CH ₃	CN	H
B-86.	OCH ₂ F	3-OCH ₃	CN	H
B-87.	OCH ₂ F	5-F	CN	H
B-88.	OCH ₂ F	5-CH ₃	CN	H
B-89.	OCH ₂ F	5-OCH ₃	CN	H
B-90.	OCH ₂ F	6-F	CN	H
B-91.	OCH ₂ F	6-CH ₃	CN	H

124

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-92.	OCH ₂ F	6-OCH ₃	CN	H
B-93.	OCHF ₂	3-F	CN	H
B-94.	OCHF ₂	3-CH ₃	CN	H
B-95.	OCHF ₂	3-OCH ₃	CN	H
B-96.	OCHF ₂	5-F	CN	H
B-97.	OCHF ₂	5-CH ₃	CN	H
B-98.	OCHF ₂	5-OCH ₃	CN	H
B-99.	OCHF ₂	6-F	CN	H
B-100.	OCHF ₂	6-CH ₃	CN	H
B-101.	OCHF ₂	6-OCH ₃	CN	H
B-102.	OCF ₃	3-F	CN	H
B-103.	OCF ₃	3-CH ₃	CN	H
B-104.	OCF ₃	3-OCH ₃	CN	H
B-105.	OCF ₃	5-F	CN	H
B-106.	OCF ₃	5-CH ₃	CN	H
B-107.	OCF ₃	5-OCH ₃	CN	H
B-108.	OCF ₃	6-F	CN	H
B-109.	OCF ₃	6-CH ₃	CN	H
B-110.	OCF ₃	6-OCH ₃	CN	H
B-111.	H	H	F	H
B-112.	F	H	F	H
B-113.	CH ₃	H	F	H
B-114.	OCH ₃	H	F	H
B-115.	CN	H	F	H
B-116.	CH ₂ F	H	F	H
B-117.	CHF ₂	H	F	H
B-118.	CF ₃	H	F	H
B-119.	OCH ₂ F	H	F	H
B-120.	OCHF ₂	H	F	H
B-121.	OCF ₃	H	F	H
B-122.	H	3-F	F	H
B-123.	H	3-CH ₃	F	H
B-124.	H	3-OCH ₃	F	H
B-125.	H	5-F	F	H
B-126.	H	5-CH ₃	F	H
B-127.	H	5-OCH ₃	F	H
B-128.	H	6-F	F	H
B-129.	H	6-CH ₃	F	H
B-130.	H	6-OCH ₃	F	H
B-131.	F	3-F	F	H
B-132.	F	3-CH ₃	F	H
B-133.	F	3-OCH ₃	F	H
B-134.	F	5-F	F	H
B-135.	F	5-CH ₃	F	H
B-136.	F	5-OCH ₃	F	H
B-137.	F	6-F	F	H
B-138.	F	6-CH ₃	F	H
B-139.	F	6-OCH ₃	F	H
B-140.	CH ₃	3-F	F	H
B-141.	CH ₃	3-CH ₃	F	H
B-142.	CH ₃	3-OCH ₃	F	H
B-143.	CH ₃	5-F	F	H
B-144.	CH ₃	5-CH ₃	F	H
B-145.	CH ₃	5-OCH ₃	F	H
B-146.	CH ₃	6-F	F	H
B-147.	CH ₃	6-CH ₃	F	H
B-148.	CH ₃	6-OCH ₃	F	H
B-149.	OCH ₃	3-F	F	H
B-150.	OCH ₃	3-CH ₃	F	H
B-151.	OCH ₃	3-OCH ₃	F	H
B-152.	OCH ₃	5-F	F	H
B-153.	OCH ₃	5-CH ₃	F	H
B-154.	OCH ₃	5-OCH ₃	F	H
B-155.	OCH ₃	6-F	F	H
B-156.	OCH ₃	6-CH ₃	F	H
B-157.	OCH ₃	6-OCH ₃	F	H
B-158.	CN	3-F	F	H
B-159.	CN	3-CH ₃	F	H
B-160.	CN	3-OCH ₃	F	H
B-161.	CN	5-F	F	H
B-162.	CN	5-CH ₃	F	H
B-163.	CN	5-OCH ₃	F	H
B-164.	CN	6-F	F	H
B-165.	CN	6-CH ₃	F	H
B-166.	CN	6-OCH ₃	F	H
B-167.	CH ₂ F	3-F	F	H
B-168.	CH ₂ F	3-CH ₃	F	H
B-169.	CH ₂ F	3-OCH ₃	F	H

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-170.	CH ₂ F	5-F	F	H
B-171.	CH ₂ F	5-CH ₃	F	H
B-172.	CH ₂ F	5-OCH ₃	F	H
B-173.	CH ₂ F	6-F	F	H
B-174.	CH ₂ F	6-CH ₃	F	H
B-175.	CH ₂ F	6-OCH ₃	F	H
B-176.	CHF ₂	3-F	F	H
B-177.	CHF ₂	3-CH ₃	F	H
B-178.	CHF ₂	3-OCH ₃	F	H
B-179.	CHF ₂	5-F	F	H
B-180.	CHF ₂	5-CH ₃	F	H
B-181.	CHF ₂	5-OCH ₃	F	H
B-182.	CHF ₂	6-F	F	H
B-183.	CHF ₂	6-CH ₃	F	H
B-184.	CHF ₂	6-OCH ₃	F	H
B-185.	CF ₃	3-F	F	H
B-186.	CF ₃	3-CH ₃	F	H
B-187.	CF ₃	3-OCH ₃	F	H
B-188.	CF ₃	5-F	F	H
B-189.	CF ₃	5-CH ₃	F	H
B-190.	CF ₃	5-OCH ₃	F	H
B-191.	CF ₃	6-F	F	H
B-192.	CF ₃	6-CH ₃	F	H
B-193.	CF ₃	6-OCH ₃	F	H
B-194.	OCH ₂ F	3-F	F	H
B-195.	OCH ₂ F	3-CH ₃	F	H
B-196.	OCH ₂ F	3-OCH ₃	F	H
B-197.	OCH ₂ F	5-F	F	H
B-198.	OCH ₂ F	5-CH ₃	F	H
B-199.	OCH ₂ F	5-OCH ₃	F	H
B-200.	OCH ₂ F	6-F	F	H
B-201.	OCH ₂ F	6-CH ₃	F	H
B-202.	OCH ₂ F	6-OCH ₃	F	H
B-203.	OCHF ₂	3-F	F	H
B-204.	OCHF ₂	3-CH ₃	F	H
B-205.	OCHF ₂	3-OCH ₃	F	H
B-206.	OCHF ₂	5-F	F	H
B-207.	OCHF ₂	5-CH ₃	F	H
B-208.	OCHF ₂	5-OCH ₃	F	H
B-209.	OCHF ₂	6-F	F	H
B-210.	OCHF ₂	6-CH ₃	F	H
B-211.	OCHF ₂	6-OCH ₃	F	H
B-212.	OCF ₃	3-F	F	H
B-213.	OCF ₃	3-CH ₃	F	H
B-214.	OCF ₃	3-OCH ₃	F	H
B-215.	OCF ₃	5-F	F	H
B-216.	OCF ₃	5-CH ₃	F	H
B-217.	OCF ₃	5-OCH ₃	F	H
B-218.	OCF ₃	6-F	F	H
B-219.	OCF ₃	6-CH ₃	F	H
B-220.	OCF ₃	6-OCH ₃	F	H
B-221.	H	H	Cl	H
B-222.	F	H	Cl	H
B-223.	CH ₃	H	Cl	H
B-224.	OCH ₃	H	Cl	H
B-225.	CN	H	Cl	H
B-226.	CH ₂ F	H	Cl	H
B-227.	CHF ₂	H	Cl	H
B-228.	CF ₃	H	Cl	H
B-229.	OCH ₂ F	H	Cl	H
B-230.	OCHF ₂	H	Cl	H
B-231.	OCF ₃	H	Cl	H
B-232.	H	3-F	Cl	H
B-233.	H	3-CH ₃	Cl	H
B-234.	H	3-OCH ₃	Cl	H
B-235.	H	5-F	Cl	H
B-236.	H	5-CH ₃	Cl	H
B-237.	H	5-OCH ₃	Cl	H
B-238.	H	6-F	Cl	H
B-239.	H	6-CH ₃	Cl	H
B-240.	H	6-OCH ₃	Cl	H
B-241.	F	3-F	Cl	H
B-242.	F	3-CH ₃	Cl	H
B-243.	F	3-OCH ₃	Cl	H
B-244.	F	5-F	Cl	H
B-245.	F	5-CH ₃	Cl	H
B-246.	F	5-OCH ₃	Cl	H
B-247.	F	6-F	Cl	H

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-248.	F	6-CH ₃	Cl	H
B-249.	F	6-OCH ₃	Cl	H
B-250.	CH ₃	3-F	Cl	H
B-251.	CH ₃	3-CH ₃	Cl	H
B-252.	CH ₃	3-OCH ₃	Cl	H
B-253.	CH ₃	5-F	Cl	H
B-254.	CH ₃	5-CH ₃	Cl	H
B-255.	CH ₃	5-OCH ₃	Cl	H
B-256.	CH ₃	6-F	Cl	H
B-257.	CH ₃	6-CH ₃	Cl	H
B-258.	CH ₃	6-OCH ₃	Cl	H
B-259.	OCH ₃	3-F	Cl	H
B-260.	OCH ₃	3-CH ₃	Cl	H
B-261.	OCH ₃	3-OCH ₃	Cl	H
B-262.	OCH ₃	5-F	Cl	H
B-263.	OCH ₃	5-CH ₃	Cl	H
B-264.	OCH ₃	5-OCH ₃	Cl	H
B-265.	OCH ₃	6-F	Cl	H
B-266.	OCH ₃	6-CH ₃	Cl	H
B-267.	OCH ₃	6-OCH ₃	Cl	H
B-268.	CN	3-F	Cl	H
B-269.	CN	3-CH ₃	Cl	H
B-270.	CN	3-OCH ₃	Cl	H
B-271.	CN	5-F	Cl	H
B-272.	CN	5-CH ₃	Cl	H
B-273.	CN	5-OCH ₃	Cl	H
B-274.	CN	6-F	Cl	H
B-275.	CN	6-CH ₃	Cl	H
B-276.	CN	6-OCH ₃	Cl	H
B-277.	CH ₂ F	3-F	Cl	H
B-278.	CH ₂ F	3-CH ₃	Cl	H
B-279.	CH ₂ F	3-OCH ₃	Cl	H
B-280.	CH ₂ F	5-F	Cl	H
B-281.	CH ₂ F	5-CH ₃	Cl	H
B-282.	CH ₂ F	5-OCH ₃	Cl	H
B-283.	CH ₂ F	6-F	Cl	H
B-284.	CH ₂ F	6-CH ₃	Cl	H
B-285.	CH ₂ F	6-OCH ₃	Cl	H
B-286.	CHF ₂	3-F	Cl	H
B-287.	CHF ₂	3-CH ₃	Cl	H
B-288.	CHF ₂	3-OCH ₃	Cl	H
B-289.	CHF ₂	5-F	Cl	H
B-290.	CHF ₂	5-CH ₃	Cl	H
B-291.	CHF ₂	5-OCH ₃	Cl	H
B-292.	CHF ₂	6-F	Cl	H
B-293.	CHF ₂	6-CH ₃	Cl	H
B-294.	CHF ₂	6-OCH ₃	Cl	H
B-295.	CF ₃	3-F	Cl	H
B-296.	CF ₃	3-CH ₃	Cl	H
B-297.	CF ₃	3-OCH ₃	Cl	H
B-298.	CF ₃	5-F	Cl	H
B-299.	CF ₃	5-CH ₃	Cl	H
B-300.	CF ₃	5-OCH ₃	Cl	H
B-301.	CF ₃	6-F	Cl	H
B-302.	CF ₃	6-CH ₃	Cl	H
B-303.	CF ₃	6-OCH ₃	Cl	H
B-304.	OCH ₂ F	3-F	Cl	H
B-305.	OCH ₂ F	3-CH ₃	Cl	H
B-306.	OCH ₂ F	3-OCH ₃	Cl	H
B-307.	OCH ₂ F	5-F	Cl	H
B-308.	OCH ₂ F	5-CH ₃	Cl	H
B-309.	OCH ₂ F	5-OCH ₃	Cl	H
B-310.	OCH ₂ F	6-F	Cl	H
B-311.	OCH ₂ F	6-CH ₃	Cl	H
B-312.	OCH ₂ F	6-OCH ₃	Cl	H
B-313.	OCHF ₂	3-F	Cl	H
B-314.	OCHF ₂	3-CH ₃	Cl	H
B-315.	OCHF ₂	3-OCH ₃	Cl	H
B-316.	OCHF ₂	5-F	Cl	H
B-317.	OCHF ₂	5-CH ₃	Cl	H
B-318.	OCHF ₂	5-OCH ₃	Cl	H
B-319.	OCHF ₂	6-F	Cl	H
B-320.	OCHF ₂	6-CH ₃	Cl	H
B-321.	OCHF ₂	6-OCH ₃	Cl	H
B-322.	OCF ₃	3-F	Cl	H
B-323.	OCF ₃	3-CH ₃	Cl	H
B-324.	OCF ₃	3-OCH ₃	Cl	H
B-325.	OCF ₃	5-F	Cl	H

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-326.	OCF ₃	5-CH ₃	Cl	H
B-327.	OCF ₃	5-OCH ₃	Cl	H
B-328.	OCF ₃	6-F	Cl	H
B-329.	OCF ₃	6-CH ₃	Cl	H
B-330.	OCF ₃	6-OCH ₃	Cl	H
B-331.	H	H	CN	F
B-332.	F	H	CN	F
B-333.	CH ₃	H	CN	F
B-334.	OCH ₃	H	CN	F
B-335.	CN	H	CN	F
B-336.	CH ₂ F	H	CN	F
B-337.	CHF ₂	H	CN	F
B-338.	CF ₃	H	CN	F
B-339.	OCH ₂ F	H	CN	F
B-340.	OCHF ₂	H	CN	F
B-341.	OCF ₃	H	CN	F
B-342.	H	3-F	CN	F
B-343.	H	3-CH ₃	CN	F
B-344.	H	3-OCH ₃	CN	F
B-345.	H	5-F	CN	F
B-346.	H	5-CH ₃	CN	F
B-347.	H	5-OCH ₃	CN	F
B-348.	H	6-F	CN	F
B-349.	H	6-CH ₃	CN	F
B-350.	H	6-OCH ₃	CN	F
B-351.	F	3-F	CN	F
B-352.	F	3-CH ₃	CN	F
B-353.	F	3-OCH ₃	CN	F
B-354.	F	5-F	CN	F
B-355.	F	5-CH ₃	CN	F
B-356.	F	5-OCH ₃	CN	F
B-357.	F	6-F	CN	F
B-358.	F	6-CH ₃	CN	F
B-359.	F	6-OCH ₃	CN	F
B-360.	CH ₃	3-F	CN	F
B-361.	CH ₃	3-CH ₃	CN	F
B-362.	CH ₃	3-OCH ₃	CN	F
B-363.	CH ₃	5-F	CN	F
B-364.	CH ₃	5-CH ₃	CN	F
B-365.	CH ₃	5-OCH ₃	CN	F
B-366.	CH ₃	6-F	CN	F
B-367.	CH ₃	6-CH ₃	CN	F
B-368.	CH ₃	6-OCH ₃	CN	F
B-369.	OCH ₃	3-F	CN	F
B-370.	OCH ₃	3-CH ₃	CN	F
B-371.	OCH ₃	3-OCH ₃	CN	F
B-372.	OCH ₃	5-F	CN	F
B-373.	OCH ₃	5-CH ₃	CN	F
B-374.	OCH ₃	5-OCH ₃	CN	F
B-375.	OCH ₃	6-F	CN	F
B-376.	OCH ₃	6-CH ₃	CN	F
B-377.	OCH ₃	6-OCH ₃	CN	F
B-378.	CN	3-F	CN	F
B-379.	CN	3-CH ₃	CN	F
B-380.	CN	3-OCH ₃	CN	F
B-381.	CN	5-F	CN	F
B-382.	CN	5-CH ₃	CN	F
B-383.	CN	5-OCH ₃	CN	F
B-384.	CN	6-F	CN	F
B-385.	CN	6-CH ₃	CN	F
B-386.	CN	6-OCH ₃	CN	F
B-387.	CH ₂ F	3-F	CN	F
B-388.	CH ₂ F	3-CH ₃	CN	F
B-389.	CH ₂ F	3-OCH ₃	CN	F
B-390.	CH ₂ F	5-F	CN	F
B-391.	CH ₂ F	5-CH ₃	CN	F
B-392.	CH ₂ F	5-OCH ₃	CN	F
B-393.	CH ₂ F	6-F	CN	F
B-394.	CH ₂ F	6-CH ₃	CN	F
B-395.	CH ₂ F	6-OCH ₃	CN	F
B-396.	CHF ₂	3-F	CN	F
B-397.	CHF ₂	3-CH ₃	CN	F
B-398.	CHF ₂	3-OCH ₃	CN	F
B-399.	CHF ₂	5-F	CN	F
B-400.	CHF ₂	5-CH ₃	CN	F
B-401.	CHF ₂	5-OCH ₃	CN	F
B-402.	CHF ₂	6-F	CN	F
B-403.	CHF ₂	6-CH ₃	CN	F

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-404.	CHF ₂	6-OCH ₃	CN	F
B-405.	CF ₃	3-F	CN	F
B-406.	CF ₃	3-CH ₃	CN	F
B-407.	CF ₃	3-OCH ₃	CN	F
B-408.	CF ₃	5-F	CN	F
B-409.	CF ₃	5-CH ₃	CN	F
B-410.	CF ₃	5-OCH ₃	CN	F
B-411.	CF ₃	6-F	CN	F
B-412.	CF ₃	6-CH ₃	CN	F
B-413.	CF ₃	6-OCH ₃	CN	F
B-414.	OCH ₂ F	3-F	CN	F
B-415.	OCH ₂ F	3-CH ₃	CN	F
B-416.	OCH ₂ F	3-OCH ₃	CN	F
B-417.	OCH ₂ F	5-F	CN	F
B-418.	OCH ₂ F	5-CH ₃	CN	F
B-419.	OCH ₂ F	5-OCH ₃	CN	F
B-420.	OCH ₂ F	6-F	CN	F
B-421.	OCH ₂ F	6-CH ₃	CN	F
B-422.	OCH ₂ F	6-OCH ₃	CN	F
B-423.	OCHF ₂	3-F	CN	F
B-424.	OCHF ₂	3-CH ₃	CN	F
B-425.	OCHF ₂	3-OCH ₃	CN	F
B-426.	OCHF ₂	5-F	CN	F
B-427.	OCHF ₂	5-CH ₃	CN	F
B-428.	OCHF ₂	5-OCH ₃	CN	F
B-429.	OCHF ₂	6-F	CN	F
B-430.	OCHF ₂	6-CH ₃	CN	F
B-431.	OCHF ₂	6-OCH ₃	CN	F
B-432.	OCF ₃	3-F	CN	F
B-433.	OCF ₃	3-CH ₃	CN	F
B-434.	OCF ₃	3-OCH ₃	CN	F
B-435.	OCF ₃	5-F	CN	F
B-436.	OCF ₃	5-CH ₃	CN	F
B-437.	OCF ₃	5-OCH ₃	CN	F
B-438.	OCF ₃	6-F	CN	F
B-439.	OCF ₃	6-CH ₃	CN	F
B-440.	OCF ₃	6-OCH ₃	CN	F
B-441.	H	H	F	F
B-442.	F	H	F	F
B-443.	CH ₃	H	F	F
B-444.	OCH ₃	H	F	F
B-445.	CN	H	F	F
B-446.	CH ₂ F	H	F	F
B-447.	CHF ₂	H	F	F
B-448.	CF ₃	H	F	F
B-449.	OCH ₂ F	H	F	F
B-450.	OCHF ₂	H	F	F
B-451.	OCF ₃	H	F	F
B-452.	H	3-F	F	F
B-453.	H	3-CH ₃	F	F
B-454.	H	3-OCH ₃	F	F
B-455.	H	5-F	F	F
B-456.	H	5-CH ₃	F	F
B-457.	H	5-OCH ₃	F	F
B-458.	H	6-F	F	F
B-459.	H	6-CH ₃	F	F
B-460.	H	6-OCH ₃	F	F
B-461.	F	3-F	F	F
B-462.	F	3-CH ₃	F	F
B-463.	F	3-OCH ₃	F	F
B-464.	F	5-F	F	F
B-465.	F	5-CH ₃	F	F
B-466.	F	5-OCH ₃	F	F
B-467.	F	6-F	F	F
B-468.	F	6-CH ₃	F	F
B-469.	F	6-OCH ₃	F	F
B-470.	CH ₃	3-F	F	F
B-471.	CH ₃	3-CH ₃	F	F
B-472.	CH ₃	3-OCH ₃	F	F
B-473.	CH ₃	5-F	F	F
B-474.	CH ₃	5-CH ₃	F	F
B-475.	CH ₃	5-OCH ₃	F	F
B-476.	CH ₃	6-F	F	F
B-477.	CH ₃	6-CH ₃	F	F
B-478.	CH ₃	6-OCH ₃	F	F
B-479.	OCH ₃	3-F	F	F
B-480.	OCH ₃	3-CH ₃	F	F
B-481.	OCH ₃	3-OCH ₃	F	F

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²	
B-482.	OCH ₃	5-F	F	F	
B-483.	OCH ₃	5-CH ₃	F	F	5
B-484.	OCH ₃	5-OCH ₃	F	F	
B-485.	OCH ₃	6-F	F	F	
B-486.	OCH ₃	6-CH ₃	F	F	
B-487.	OCH ₃	6-OCH ₃	F	F	
B-488.	CN	3-F	F	F	
B-489.	CN	3-CH ₃	F	F	10
B-490.	CN	3-OCH ₃	F	F	
B-491.	CN	5-F	F	F	
B-492.	CN	5-CH ₃	F	F	
B-493.	CN	5-OCH ₃	F	F	
B-494.	CN	6-F	F	F	
B-495.	CN	6-CH ₃	F	F	
B-496.	CN	6-OCH ₃	F	F	15
B-497.	CH ₂ F	3-F	F	F	
B-498.	CH ₂ F	3-CH ₃	F	F	
B-499.	CH ₂ F	3-OCH ₃	F	F	
B-500.	CH ₂ F	5-F	F	F	
B-501.	CH ₂ F	5-CH ₃	F	F	
B-502.	CH ₂ F	5-OCH ₃	F	F	20
B-503.	CH ₂ F	6-F	F	F	
B-504.	CH ₂ F	6-CH ₃	F	F	
B-505.	CH ₂ F	6-OCH ₃	F	F	
B-506.	CHF ₂	3-F	F	F	
B-507.	CHF ₂	3-CH ₃	F	F	
B-508.	CHF ₂	3-OCH ₃	F	F	25
B-509.	CHF ₂	5-F	F	F	
B-510.	CHF ₂	5-CH ₃	F	F	
B-511.	CHF ₂	5-OCH ₃	F	F	
B-512.	CHF ₂	6-F	F	F	
B-513.	CHF ₂	6-CH ₃	F	F	
B-514.	CHF ₂	6-OCH ₃	F	F	30
B-515.	CF ₃	3-F	F	F	
B-516.	CF ₃	3-CH ₃	F	F	
B-517.	CF ₃	3-OCH ₃	F	F	
B-518.	CF ₃	5-F	F	F	
B-519.	CF ₃	5-CH ₃	F	F	
B-520.	CF ₃	5-OCH ₃	F	F	
B-521.	CF ₃	6-F	F	F	35
B-522.	CF ₃	6-CH ₃	F	F	
B-523.	CF ₃	6-OCH ₃	F	F	
B-524.	OCH ₂ F	3-F	F	F	
B-525.	OCH ₂ F	3-CH ₃	F	F	
B-526.	OCH ₂ F	3-OCH ₃	F	F	
B-527.	OCH ₂ F	5-F	F	F	40
B-528.	OCH ₂ F	5-CH ₃	F	F	
B-529.	OCH ₂ F	5-OCH ₃	F	F	
B-530.	OCH ₂ F	6-F	F	F	
B-531.	OCH ₂ F	6-CH ₃	F	F	
B-532.	OCH ₂ F	6-OCH ₃	F	F	
B-533.	OCHF ₂	3-F	F	F	45
B-534.	OCHF ₂	3-CH ₃	F	F	
B-535.	OCHF ₂	3-OCH ₃	F	F	
B-536.	OCHF ₂	5-F	F	F	
B-537.	OCHF ₂	5-CH ₃	F	F	
B-538.	OCHF ₂	5-OCH ₃	F	F	
B-539.	OCHF ₂	6-F	F	F	50
B-540.	OCHF ₂	6-CH ₃	F	F	
B-541.	OCHF ₂	6-OCH ₃	F	F	
B-542.	OCF ₃	3-F	F	F	
B-543.	OCF ₃	3-CH ₃	F	F	
B-544.	OCF ₃	3-OCH ₃	F	F	
B-545.	OCF ₃	5-F	F	F	55
B-546.	OCF ₃	5-CH ₃	F	F	
B-547.	OCF ₃	5-OCH ₃	F	F	
B-548.	OCF ₃	6-F	F	F	
B-549.	OCF ₃	6-CH ₃	F	F	
B-550.	OCF ₃	6-OCH ₃	F	F	
B-551.	H	H	Cl	F	
B-552.	F	H	Cl	F	60
B-553.	CH ₃	H	Cl	F	
B-554.	OCH ₃	H	Cl	F	
B-555.	CN	H	Cl	F	
B-556.	CH ₂ F	H	Cl	F	
B-557.	CHF ₂	H	Cl	F	
B-558.	CF ₃	H	Cl	F	65
B-559.	OCH ₂ F	H	Cl	F	

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-560.	OCHF ₂	H	Cl	F
B-561.	OCF ₃	H	Cl	F
B-562.	H	3-F	Cl	F
B-563.	H	3-CH ₃	Cl	F
B-564.	H	3-OCH ₃	Cl	F
B-565.	H	5-F	Cl	F
B-566.	H	5-CH ₃	Cl	F
B-567.	H	5-OCH ₃	Cl	F
B-568.	H	6-F	Cl	F
B-569.	H	6-CH ₃	Cl	F
B-570.	H	6-OCH ₃	Cl	F
B-571.	F	3-F	Cl	F
B-572.	F	3-CH ₃	Cl	F
B-573.	F	3-OCH ₃	Cl	F
B-574.	F	5-F	Cl	F
B-575.	F	5-CH ₃	Cl	F
B-576.	F	5-OCH ₃	Cl	F
B-577.	F	6-F	Cl	F
B-578.	F	6-CH ₃	Cl	F
B-579.	F	6-OCH ₃	Cl	F
B-580.	CH ₃	3-F	Cl	F
B-581.	CH ₃	3-CH ₃	Cl	F
B-582.	CH ₃	3-OCH ₃	Cl	F
B-583.	CH ₃	5-F	Cl	F
B-584.	CH ₃	5-CH ₃	Cl	F
B-585.	CH ₃	5-OCH ₃	Cl	F
B-586.	CH ₃	6-F	Cl	F
B-587.	CH ₃	6-CH ₃	Cl	F
B-588.	CH ₃	6-OCH ₃	Cl	F
B-589.	OCH ₃	3-F	Cl	F
B-590.	OCH ₃	3-CH ₃	Cl	F
B-591.	OCH ₃	3-OCH ₃	Cl	F
B-592.	OCH ₃	5-F	Cl	F
B-593.	OCH ₃	5-CH ₃	Cl	F
B-594.	OCH ₃	5-OCH ₃	Cl	F
B-595.	OCH ₃	6-F	Cl	F
B-596.	OCH ₃	6-CH ₃	Cl	F
B-597.	OCH ₃	6-OCH ₃	Cl	F
B-598.	CN	3-F	Cl	F
B-599.	CN	3-CH ₃	Cl	F
B-600.	CN	3-OCH ₃	Cl	F
B-601.	CN	5-F	Cl	F
B-602.	CN	5-CH ₃	Cl	F
B-603.	CN	5-OCH ₃	Cl	F
B-604.	CN	6-F	Cl	F
B-605.	CN	6-CH ₃	Cl	F
B-606.	CN	6-OCH ₃	Cl	F
B-607.	CH ₂ F	3-F	Cl	F
B-608.	CH ₂ F	3-CH ₃	Cl	F
B-609.	CH ₂ F	3-OCH ₃	Cl	F
B-610.	CH ₂ F	5-F	Cl	F
B-611.	CH ₂ F	5-CH ₃	Cl	F
B-612.	CH ₂ F	5-OCH ₃	Cl	F
B-613.	CH ₂ F	6-F	Cl	F
B-614.	CH ₂ F	6-CH ₃	Cl	F
B-615.	CH ₂ F	6-OCH ₃	Cl	F
B-616.	CHF ₂	3-F	Cl	F
B-617.	CHF ₂	3-CH ₃	Cl	F
B-618.	CHF ₂	3-OCH ₃	Cl	F
B-619.	CHF ₂	5-F	Cl	F
B-620.	CHF ₂	5-CH ₃	Cl	F
B-621.	CHF ₂	5-OCH ₃	Cl	F
B-622.	CHF ₂	6-F	Cl	F
B-623.	CHF ₂	6-CH ₃	Cl	F
B-624.	CHF ₂	6-OCH ₃	Cl	F
B-625.	CF ₃	3-F	Cl	F
B-626.	CF ₃	3-CH ₃	Cl	F
B-627.	CF ₃	3-OCH ₃	Cl	F
B-628.	CF ₃	5-F	Cl	F
B-629.	CF ₃	5-CH ₃	Cl	F
B-630.	CF ₃	5-OCH ₃	Cl	F
B-631.	CF ₃	6-F	Cl	F
B-632.	CF ₃	6-CH ₃	Cl	F
B-633.	CF ₃	6-OCH ₃	Cl	F
B-634.	OCH ₂ F	3-F	Cl	F
B-635.	OCH ₂ F	3-CH ₃	Cl	F
B-636.	OCH ₂ F	3-OCH ₃	Cl	F
B-637.	OCH ₂ F	5-F	Cl	F

TABLE B-continued

Example No.	R ^{8b}	R ^{8c}	R ¹	R ²
B-638.	OCH ₂ F	5-CH ₃	Cl	F
B-639.	OCH ₂ F	5-OCH ₃	Cl	F
B-640.	OCH ₂ F	6-F	Cl	F
B-641.	OCH ₂ F	6-CH ₃	Cl	F
B-642.	OCH ₂ F	6-OCH ₃	Cl	F
B-643.	OCHF ₂	3-F	Cl	F
B-644.	OCHF ₂	3-CH ₃	Cl	F
B-645.	OCHF ₂	3-OCH ₃	Cl	F
B-646.	OCHF ₂	5-F	Cl	F
B-647.	OCHF ₂	5-CH ₃	Cl	F
B-648.	OCHF ₂	5-OCH ₃	Cl	F
B-649.	OCHF ₂	6-F	Cl	F
B-650.	OCHF ₂	6-CH ₃	Cl	F
B-651.	OCHF ₂	6-OCH ₃	Cl	F
B-652.	OCF ₃	3-F	Cl	F
B-653.	OCF ₃	3-CH ₃	Cl	F
B-654.	OCF ₃	3-OCH ₃	Cl	F
B-655.	OCF ₃	5-F	Cl	F
B-656.	OCF ₃	5-CH ₃	Cl	F
B-657.	OCF ₃	5-OCH ₃	Cl	F
B-658.	OCF ₃	6-F	Cl	F
B-659.	OCF ₃	6-CH ₃	Cl	F
B-660.	OCF ₃	6-OCH ₃	Cl	F

The positions (e.g. 3-/5-/6-) of R³ are relative to the 2- and 4-positions of radicals R¹ and R² and to the 1-position of the attachment point of the ring to the SO₂ group.

The preferred compounds among the compounds I.1 to I.128 mentioned above are those of the formulae I.1, I.2, I.3, I.4, I.5, I.9, I.13, I.15, I.17, I.19, I.33, I.35, I.49, I.51, I.65, I.67, I.81, I.83, I.97, I.99, I.113 and I.115. More preferred are those of formulae I.1, I.3, I.17, I.19, I.33, I.35, I.49, I.51, I.65, I.67, I.81, I.83, I.97, I.99, I.113 and I.115. Particularly preferred are compounds of the formulae I.1 and I.3.

In a specific embodiment, the compounds I are selected from the compounds specified in the examples, either as a free base or in form of a pharmaceutically acceptable salt, an N-oxide or a stereoisomer or the racemate or any mixture of stereoisomers thereof.

The compounds I of the invention have a center of chirality in position 3 of the 2-oxindole ring. The compounds of the invention may therefore be in the form of a 1:1 mixture of enantiomers (racemate) or of a nonracemic mixture of enantiomers in which one of the two enantiomers, either the enantiomer which rotates the plane of vibration of linearly polarized light to the left (i.e. minus rotation) (hereinafter (-) enantiomer) or the enantiomer which rotates the plane of vibration of linearly polarized light to the right (i.e. plus rotation) (hereinafter (+) enantiomer), is enriched, or of substantially enantiopure compounds, that is to say of substantially enantiopure (-) enantiomer or (+) enantiomer. Since the compounds of the invention have a single center of asymmetry and no axis/plane of chirality, a nonracemic mixture can also be defined as a mixture of enantiomers in which either the R or the S enantiomer predominates. Substantially enantiopure compounds can accordingly also be defined as substantially enantiopure R enantiomer or substantially enantiopure S enantiomer.

"Substantially enantiopure compounds" means in the context of the present invention those compounds having an enantiomeric excess (ee; % ee=(R-S)/(R+S)×100 or (S-R)/(S+R)×100) of at least 80% ee, preferably at least 85% ee, more preferably at least 90% ee, even more preferably at least 95% ee and in particular at least 98% ee.

In one embodiment of the invention, the compounds of the invention are in the form of substantially enantiopure compounds. Particularly preferred compounds have an

enantiomeric excess of at least 85% ee, more preferably of at least 90% ee, even more preferably of at least 95% ee and in particular of at least 98% ee.

The invention thus relates both to the pure enantiomers and to mixtures thereof, e.g. mixtures in which one enantiomer is present in enriched form, but also to the racemates. The invention also relates to the pharmaceutically acceptable salts of the pure enantiomers of compounds I, and the mixtures of enantiomers in the form of the pharmaceutically acceptable salts of compounds I.

Preferred embodiments of the invention are compounds of the formula I as detailed above which are characterized in that they are in optically active form, and the enantiomer of the relevant compound of the formula I is the S-enantiomer, in the form of a free base, or a pharmaceutically acceptable salt thereof.

Particularly preference is given to compounds of the general formula I and their pharmaceutically acceptable salts as detailed above in which the corresponding S-enantiomer is present in an optical purity (enantiomeric excess, ee) of more than 50% ee, particularly preferably of at least 80% ee, more preferably of at least 90% ee and even more preferably of at least 95% ee and in particular of at least 98% ee.

Likewise preferred embodiments of the invention are compounds of the general formula I as detailed above which are characterized in that they are in optically inactive form, i.e. in the form of the racemate, or in the form of a pharmaceutically acceptable salt of the racemate.

Examples of synthetic routes for preparing the oxindole derivatives of the invention are described below.

The compounds of the invention can be prepared by using methods described in WO 2005/030755 and WO 2006/005609 for synthesizing analogous compounds, and the preparation is outlined by way of example in synthesis schemes 1 to 4. If not indicated otherwise, the variables in these synthetic schemes have the same meanings as in formula I.

The 3-hydroxy-1,3-dihydroindol-2-ones IV can be obtained by addition of metallated benzenes or heterocycles III onto the 3-keto group of the isatins II. The metallated benzenes or heterocycles, such as, for example, the corresponding Grignard (Mg) or organyllithium compound, can be obtained in any conventional way from halogen or hydrocarbon compounds. Examples of methods are present in Houben-Weyl, Methoden der Organischen Chemie, vol. 13, 1-2, chapter on Mg and Li compounds. The isatins II are either commercially available or were prepared in analogy to methods described in the literature (Advances in Heterocyclic Chemistry, A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1975, 18, 2-58; J. Brazil. Chem. Soc. 12, 273-324, 2001).

The 3-hydroxyoxindoles IV which comprise an iodine in the 6-membered aromatic ring, for example in position 5 or 6, i.e. in the position of the radicals R¹ or R², can be converted with KCN or Zn(CN)₂ with Pd(0) catalysis in solvents such as dimethylformamide or tetrahydrofuran, where appropriate also with addition of bases such as K₂CO₃ or other carbonates or amines, at elevated temperature into the analogous cyan-containing 3-hydroxyoxindole IV. Pd(0) salts which can be taken are for example transition metal complexes which are prepared in situ from PdCl₂ or PdOAc₂ by addition of phosphines such as tris(ortho-tolyl) phosphine. It is likewise possible to employ commercial palladium complexes such as, for example, the catalyst tetrakis(triphenylphosphine)palladium(0) and/or additions of phosphine ligands.

133

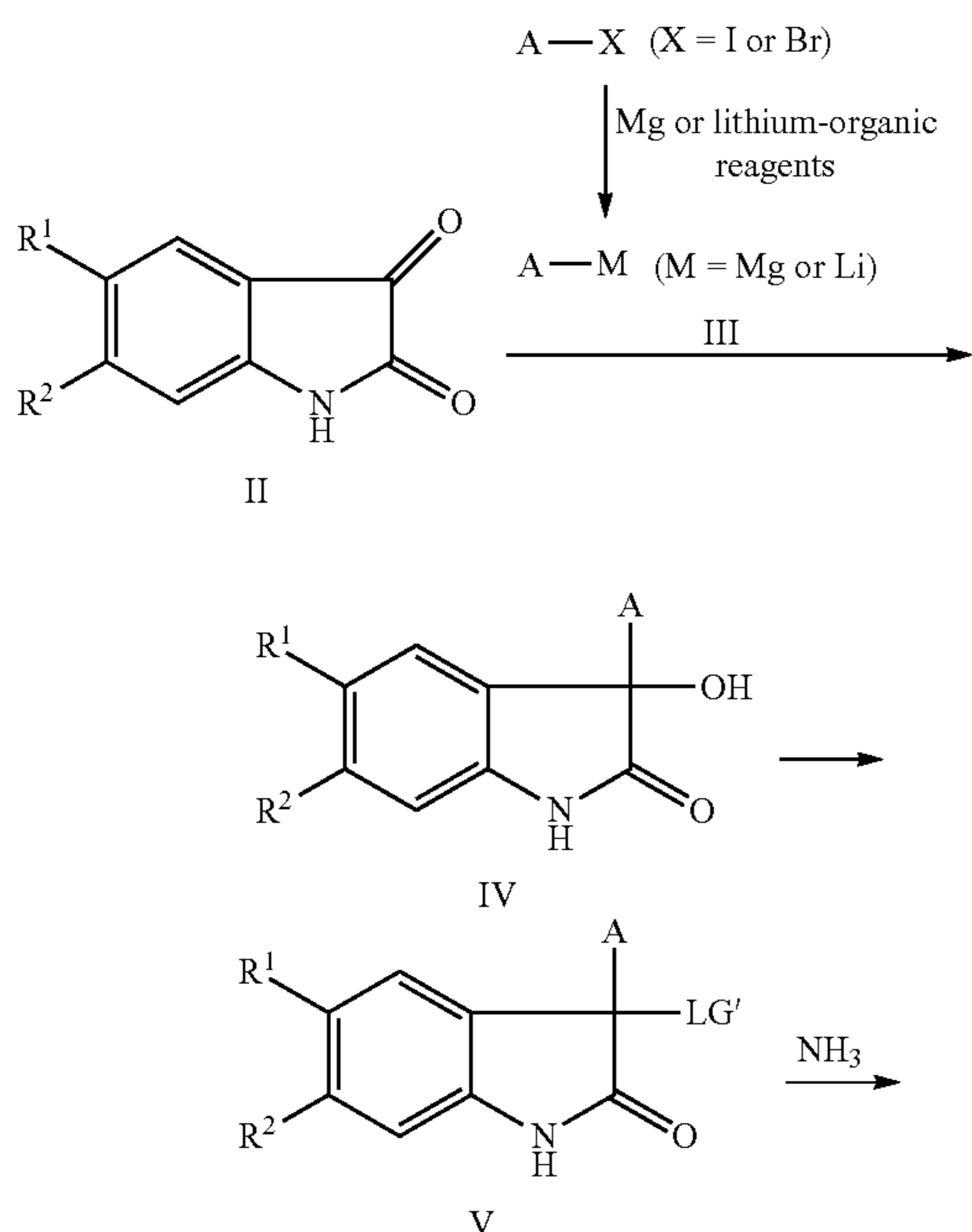
The 3-hydroxyoxindoles IV can be converted into the compounds V which have a leaving group LG' in position 3, where the leaving group LG' is a conventional leaving group such as, for example, chlorine or bromide. The intermediate V with for example LG'=chlorine can be prepared by

treating the alcohol IV with thionyl chloride in the presence of a base such as, for example, pyridine, in a suitable solvent such as, for example, dichloromethane. The compounds V can subsequently be reacted with amines, such as, for example, ammonia, in a substitution reaction to give the amines VI. The compounds VI can subsequently be converted by treatment with sulfonyl chlorides VII after deprotonation with a strong base such as, for example, potassium tert-butoxide or sodium hydride in DMF into the sulfonylated product VIII. The sulfonyl chlorides VII employed can either be purchased or be prepared by known processes (for example J. Med. Chem. 40, 1149 (1997)).

The compounds of the invention of the general formula I which have a urea group in position 3 (in other words: compounds I wherein X¹ is NH and X² is N) can be prepared as described in WO 2005/030755 and WO 2006/005609, and shown in synthesis scheme 1, in a two-stage process: firstly, the compounds VIII are reacted with phenyl chloroformate in the presence of a base such as, for example, pyridine to give the corresponding phenyl carbamate IX.

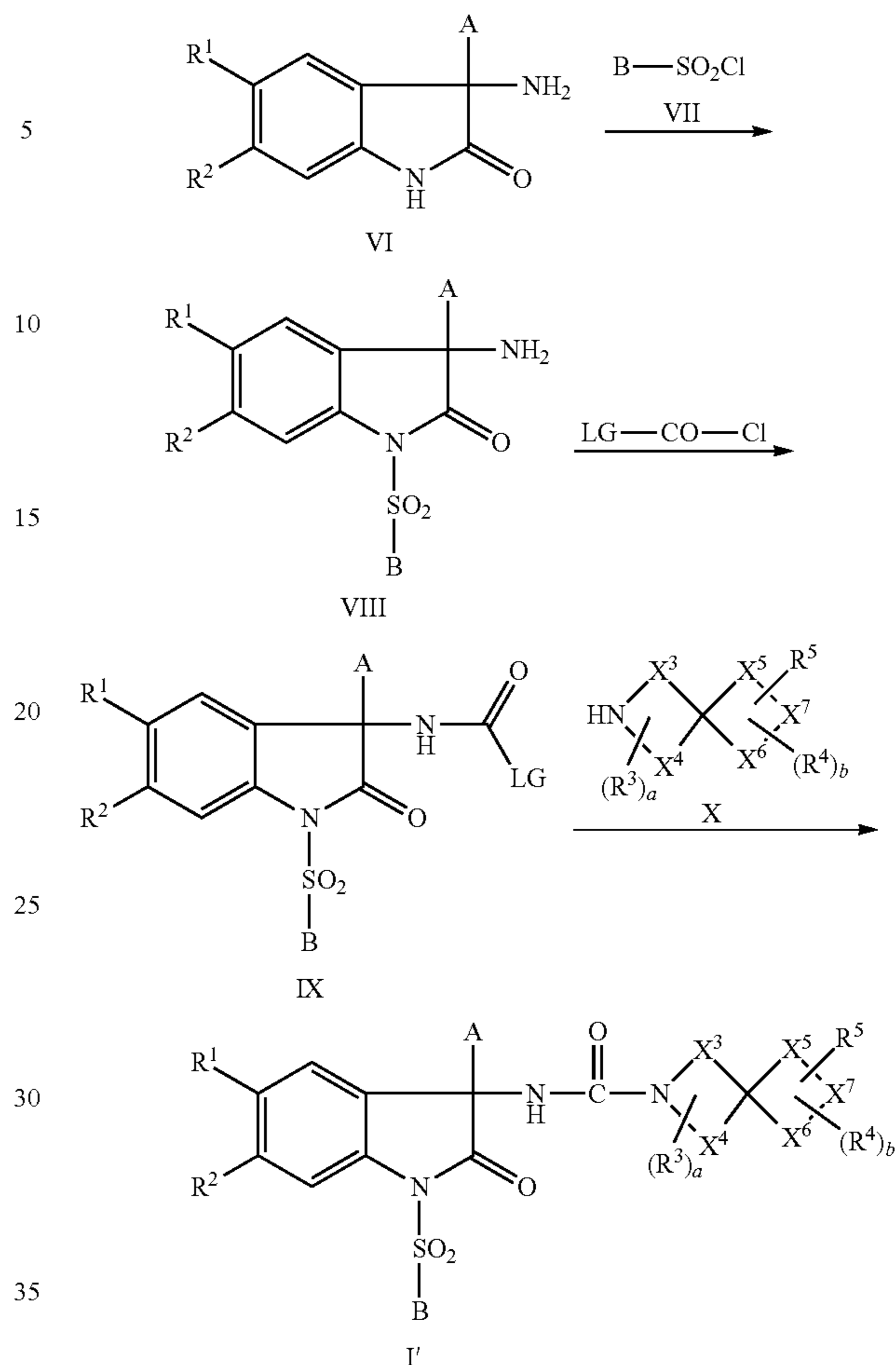
Subsequent reaction with amines X, where appropriate at elevated temperature and with the addition of auxiliary bases such as, for example, triethylamine or diisopropylethylamine, leads to the compounds of the invention of the general formula (I) with a urea bridge (X¹=NH). The amines X can be either purchased or prepared by methods known from the literature. Compounds I of the invention with R³=H can be prepared by using appropriate Boc-protected amines (R³=Boc). The Boc protective group can subsequently be removed, for example by treatment with trifluoroacetic acid in dichloromethane.

Synthesis Scheme 1



134

-continued

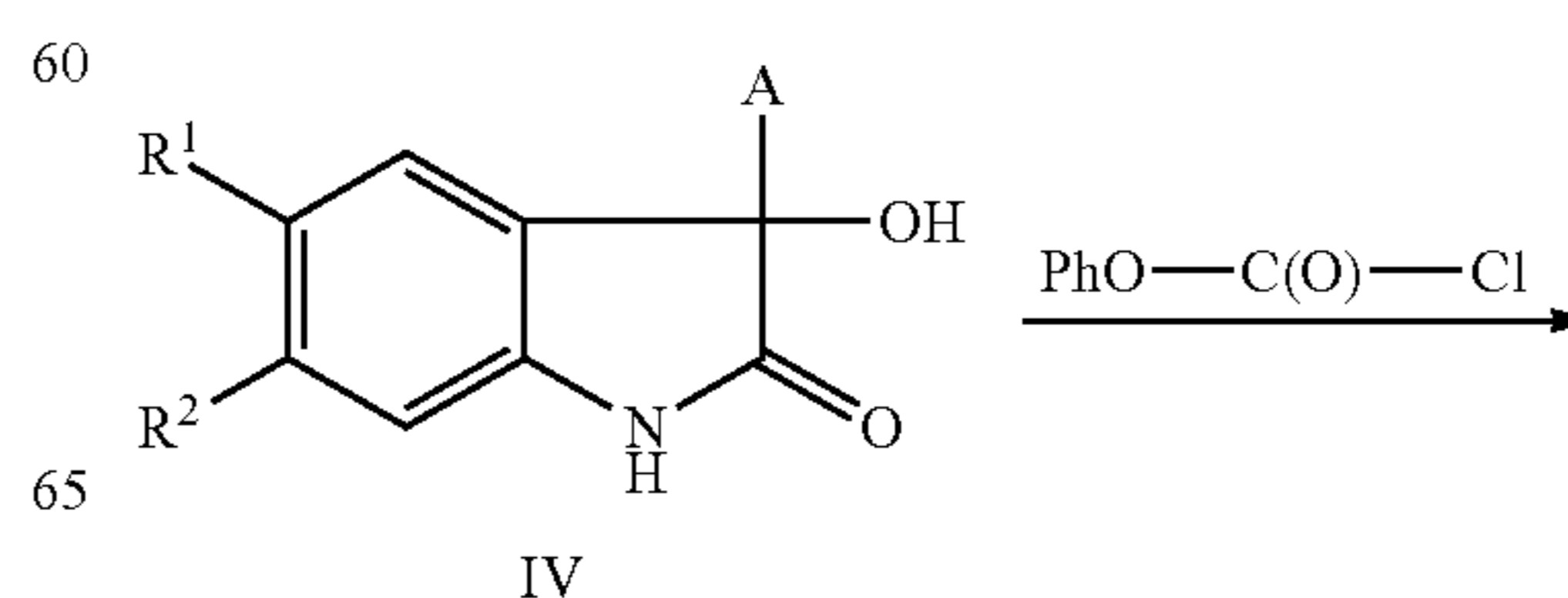


Ph = Phenyl
 LG' = leaving group, such as for example Cl
 LG = leaving group, such as for example PhO (Phenoxy)

40

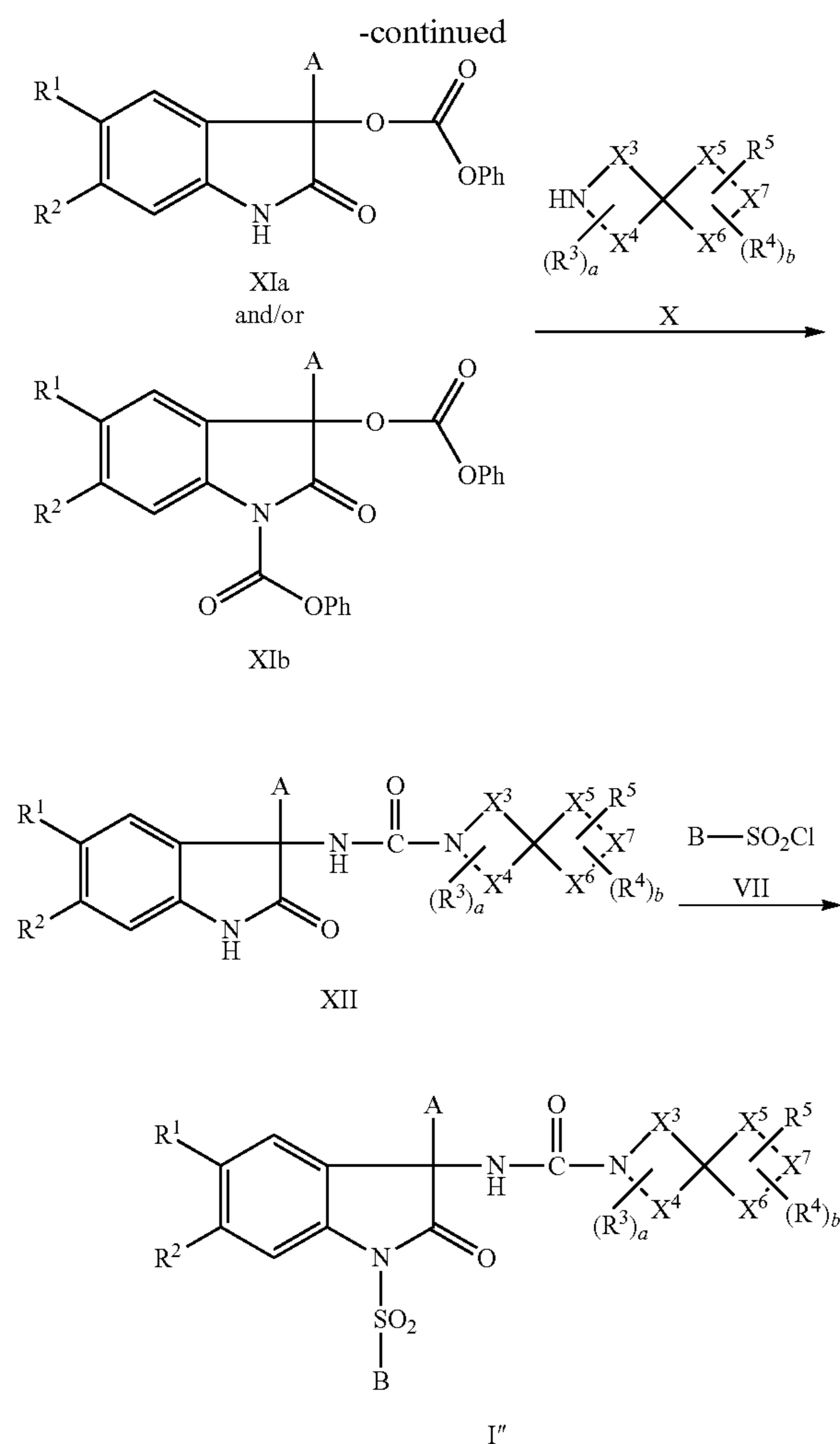
The compounds of the invention of the general formula I having a carbamate group in position 3 (in other words: compounds I wherein X¹ is O and X² is N) can be prepared as described in WO 2006/005609 and shown in synthesis scheme 2: firstly, the 3-hydroxy compound IV is reacted with phenyl chloroformate to give the phenyl carbonate derivatives XIa and/or XIb. The carbamate derivatives XII are obtained with an excess of amine X and can subsequently be converted under the usual conditions (deprotonation with a strong base such as, for example, sodium hydride or potassium tert-butoxide in a suitable solvent such as, for example, DMF, followed by treatment with sulfonyl chlorides VII) into the compounds I of the invention with a carbamate bridge.

Synthesis Scheme 2



65

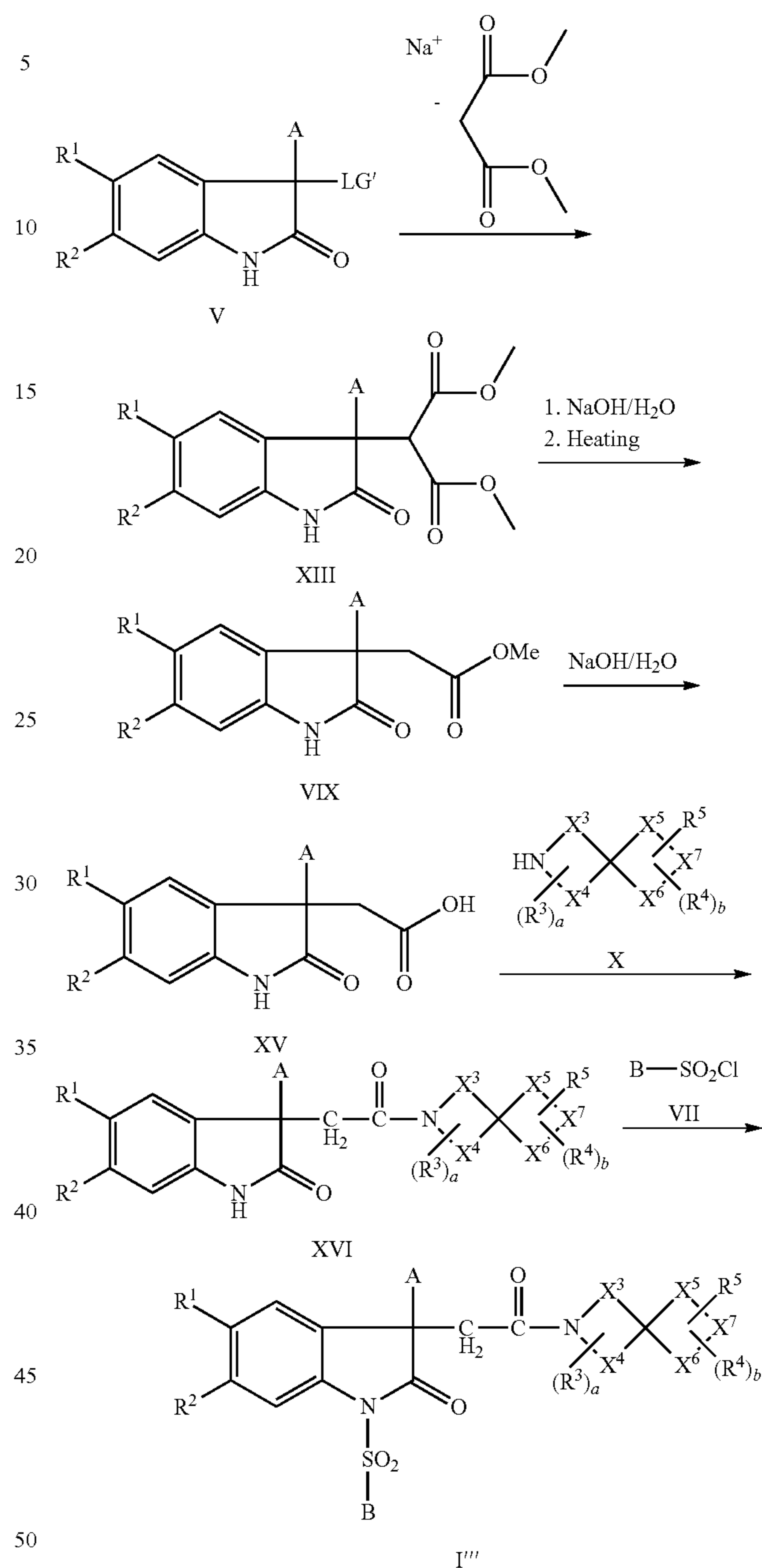
135



The compounds of the invention of the general formula I which have a 2-oxo-ethyl group in position 3 (in other words: compounds I wherein X^1 is CH_2 and X^2 is N) can be prepared as shown in synthesis scheme 3. Introduction of the acetic acid group can take place as described in WO 2006/005609 in a 4-stage sequence (1. replacement of the leaving group LG' in V by the sodium salt of dimethyl malonate, 2. hydrolysis of the first ester group, 3. thermal decarboxylation, 4. hydrolysis of the second ester group). The amine side chain X can be coupled to the carboxylic acid XV using standard coupling reagents known in peptide chemistry, such as, for example, EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole) in a solvent such as, for example, N,N-dimethylformamide, or BOP (1-benzotriazolyltris(dimethylamino)phosphonium hexafluorophosphate) in the presence of a base such as triethylamine or diisopropylethylamine. The sulfonylation can take place by deprotonation of the coupling product XVI with a strong base such as, for example, sodium hydride or potassium tert-butoxide, and subsequent treatment with sulfonyl chlorides VII in a solvent such as, for example, DMF, and leads to the compounds I of the invention with an amide bridge.

136

Synthesis Scheme 3

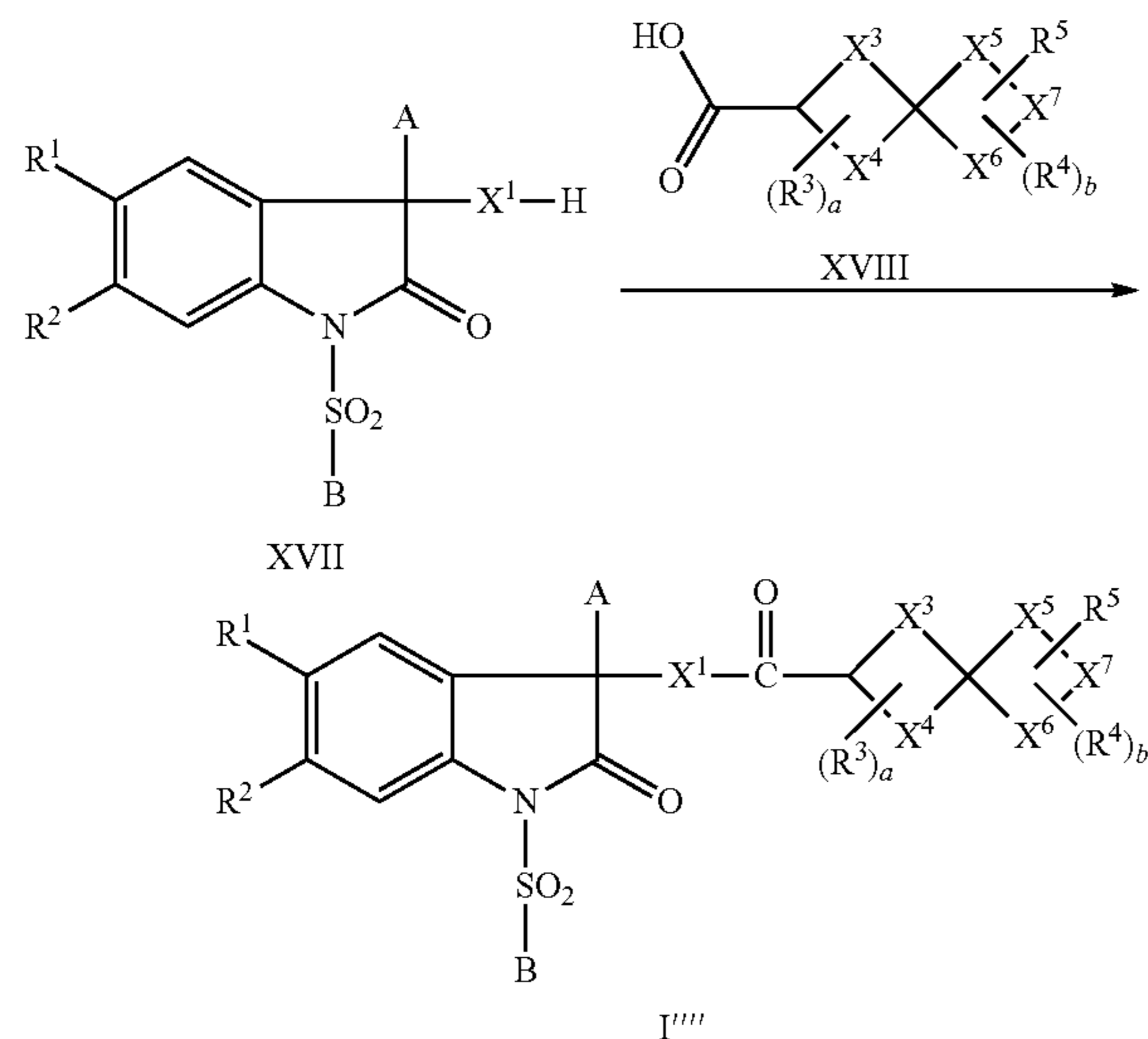


Compounds I wherein X^1 is NH or O and X^2 is CH can be prepared as shown in synthesis scheme 4 in a standard amidation or esterification process. Amidation (when X^1 is NH) can be carried out by reacting the amine XVII with the acid XVIII under heating and removal of reaction water, but is preferably carried out by activation of the carboxylic acid XVIII with oxalylchloride $[(COCl)_2]$ or thionylchloride $(SOCl_2)$ to the respective acid chloride, followed by reaction with amine XVII. Alternatively, amidation is carried out in the presence of a coupling reagent. Suitable coupling reagent (activators) are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide) and DIC (diisopropylcarbodiimide), benzo-

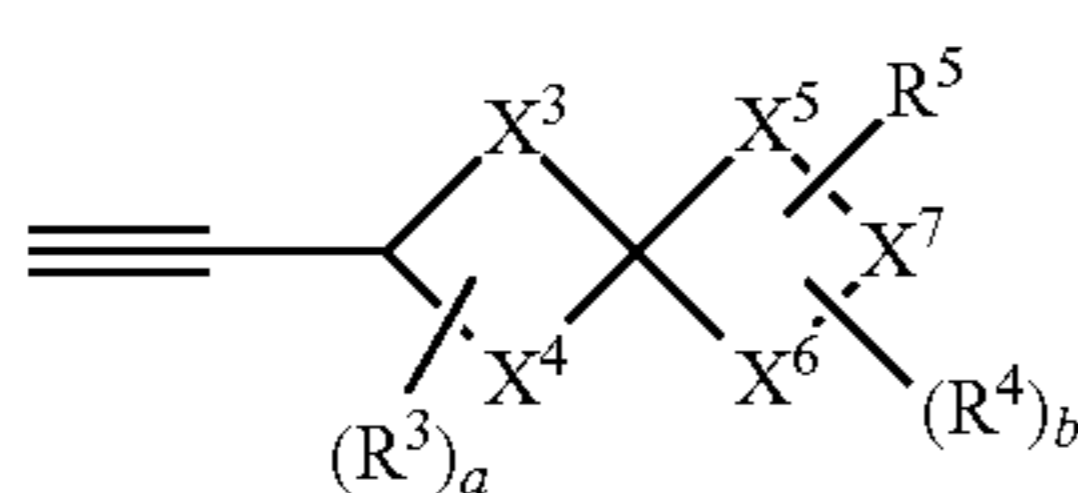
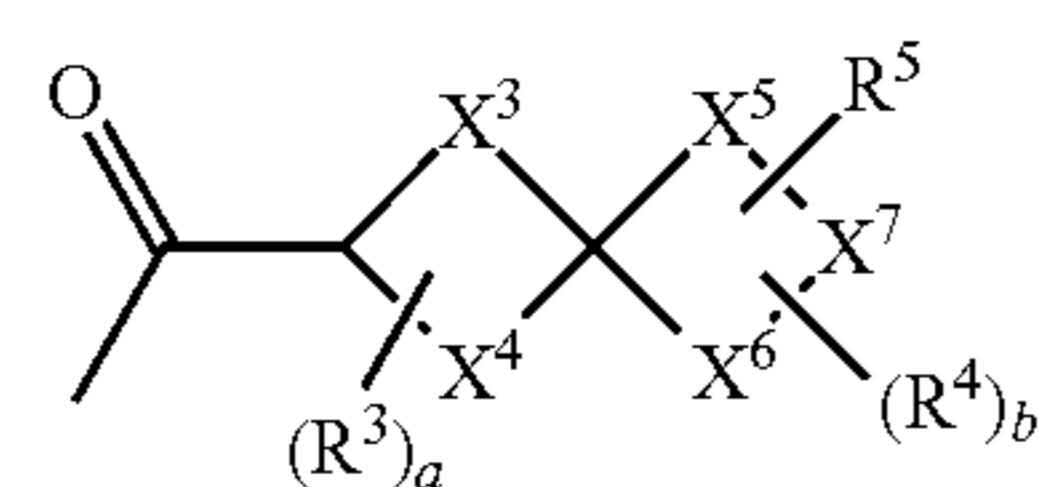
137

triazole derivatives, such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chlorotetrafluoroborate) and phosphonium-derived activators, such as BOP ((benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate), Py-BOP ((benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate) and Py-BrOP (bromotripyrrolidinophosphonium hexafluorophosphate). Generally, the activator is used in excess. The benzotriazole and phosphonium coupling reagents are generally used in a basic medium. Alike, esterification (when X¹ is O) can be carried out by reacting the alcohol XVII with the acid XVIII under heating and removal of reaction water, but is preferably carried out by activation of the carboxylic acid XVIII with oxalylchloride [(COCl)₂] or thionylchloride (SOCl₂) to the respective acid chloride, followed by reaction with alcohol XVII.

Synthesis Scheme 4



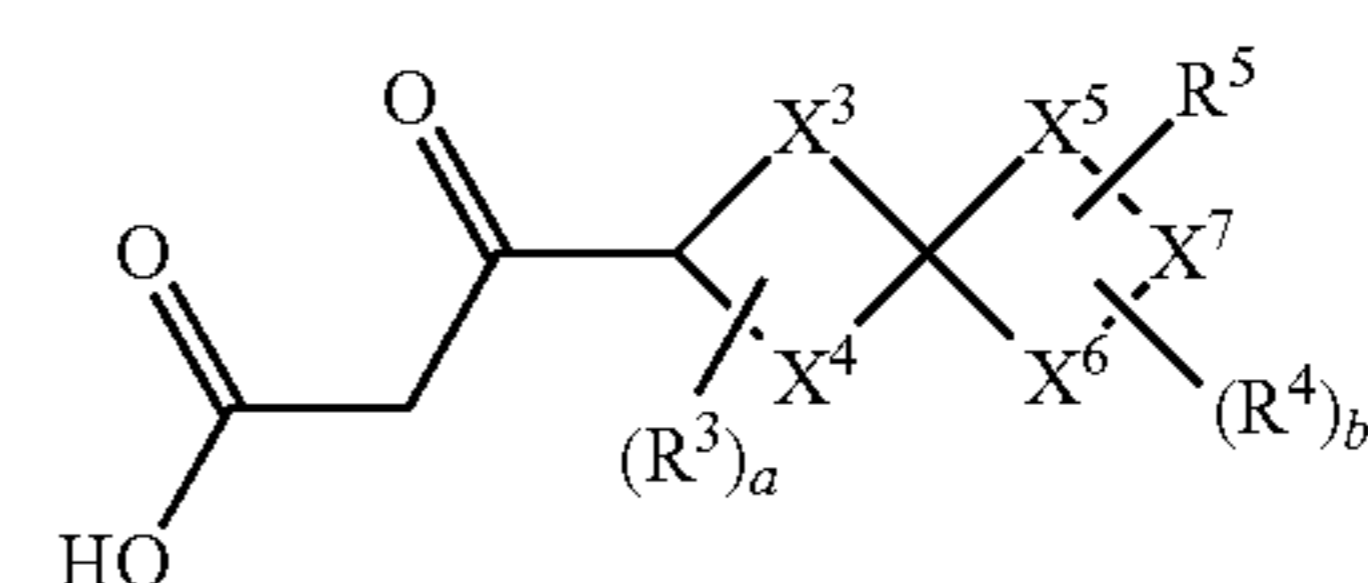
Compounds I wherein X¹ is CH₂ and X² is CH can be prepared in analogy to the synthetic routes described in Organic and Biomolecular Chemistry 2013, 11(40), 6984-6993 starting either from isatin II and the Grignard reagent A-M (III) or starting from the oxindole compounds IV or V and reacting these with either XIX or XX.



In case that XIX is used, Cu(CF₃SO₃)₂ is suitably used as catalyst, and in case that XX is used, Sn(CF₃SO₃)₂ is a suitable catalyst.

138

Compounds I wherein X¹ is CH₂ and X² is CH can also be prepared in analogy to the synthetic route described in J. Org. Chem. 2012, 77(24), 11325-11332 by decarboxylating β-ketoacid XXI in the presence of an oxindole compound V.



The sequence of reaction steps can be varied. For instance, in schemes 1 to 3, the (het)arylsulfonyl group B—SO₂— can be introduced earlier than shown, e.g. by reacting yet II, IV or V with VII in scheme 1, by reacting yet IV, XIa or XIb with VII in scheme 2 or by reacting yet V, XIII, XIV or XV with VII in scheme 3; or can be introduced later, e.g. after the introduction of X in scheme 1 or by reacting a compound XVII, which does however not carry the B—SO₂— group, with XVIII and only then with VII. Spiro compounds X can be used in protected form, if required, e.g. if one of X³, X⁴, X⁵, X⁶ and/or X⁷ is NH and is not substituted by a radical R³, R⁴ or R⁵ which confers protection to this nitrogen ring atom. Suitable protective groups are, for example, C₁-C₄-alkoxycarbonyl groups, such as tert-butoxycarbonyl (Boc), C₁-C₄-alkylcarbonyl groups, such as acetyl, C₁-C₄-alkylsulfonyl, phenylsulfonyl or benzyl. Usually, Boc is used. Moreover, radical R⁵ (if not hydrogen) can be introduced at a later point of time; especially if bound to X⁷. In this case, a compound I', I'', I''' or I''''', which does however not carry the radical R⁵ and in which X⁷ is NH, is reacted with a suitable precursor compound of R⁵ (especially if R⁵ is optionally substituted alkyl, alkenyl, alkynyl or cycloalkyl), such as R⁵—Y wherein Y is a suitable leaving group such as Cl, Br, I or the triflate group. Phenyl or heterocyclyl groups R⁵ can be introduced in a Buchwald-Hartwig reaction using a Pd catalyst.

In analogy to the findings described by Y. Naruse et al. in Tetrahedron Asymmetry 2013, 24, 169-171, the above synthetic routes may result in the formation of two conformers. If the (het)arylsulfonyl group B—SO₂— is introduced in the last step; i.e. after the spiro ring has been introduced, mostly only one conformer is obtained.

If not indicated otherwise, the above-described reactions are generally carried out in a solvent at temperatures between room temperature and the boiling temperature of the solvent employed. Alternatively, the activation energy which is required for the reaction can be introduced into the reaction mixture using microwaves, something which has proved to be of value, in particular, in the case of the reactions catalyzed by transition metals (with regard to reactions using microwaves, see Tetrahedron 2001, 57, p. 9199 ff. p. 9225 ff. and also, in a general manner, "Microwaves in Organic Synthesis", André Loupy (Ed.), Wiley-VCH 2002.

The acid addition salts of compounds I are prepared in a customary manner by mixing the free base with a corresponding acid, where appropriate in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl tert-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of

the synthetic route, protection of any chemical functionality that may not be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the preparation methods are within routine techniques.

Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention may be accomplished by methods analogous to those described in the synthetic scheme described hereinabove and in specific examples.

Starting materials, if not commercially available, may be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

The present invention moreover relates to compounds of formula I as defined above, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium, ^{12}C by ^{13}C , ^{14}N by ^{15}N , ^{16}O by ^{18}O) and preferably wherein at least one hydrogen atom has been replaced by a deuterium atom.

Of course, the unlabeled compounds according to the invention might naturally include certain amounts of these respective isotopes. Therefore, when referring to compounds I, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, it will be understood that the isotope is present in a higher amount than would naturally occur.

Stable isotopes (e.g., deuterium, ^{13}C , ^{15}N , ^{18}O) are non-radioactive isotopes which contain one additional neutron than the normally abundant isotope of the respective atom. Deuterated compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the non deuterated parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., *Advances in Drug Research* Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., *J. Labelled Comp. Radiopharmaceut.*, 36(10): 927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

Incorporation of a heavy atom, particularly substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug.

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These changes may influence the fate of the drug at different steps along its passage through the body. Absorption, distribution, metabolism or excretion can be changed. Absorption and distribution are processes that depend primarily on the molecular size and the lipophilicity of the substance. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction.

Drug metabolism can give rise to large isotopic effect if the breaking of a chemical bond to a deuterium atom is the rate limiting step in the process. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. In any reaction in which the breaking of this bond is the rate limiting step, the reaction will proceed slower for the molecule with the heavy isotope due to "kinetic isotope effect". A reaction involving breaking a C-D bond can be up to 700 percent slower than a similar reaction involving breaking a C-H bond. If the C-D bond is not involved in any of the steps leading to the metabolite, there may not be any effect to alter the behavior of the drug. If a deuterium is placed at a site involved in the metabolism of a drug, an isotope effect will be observed only if breaking of the C-D bond is the rate limiting step. There is evidence to suggest that whenever cleavage of an aliphatic C-H bond occurs, usually by oxidation catalyzed by a mixed-function oxidase, replacement of the hydrogen by deuterium will lead to observable isotope effect. It is also important to understand that the incorporation of deuterium at the site of metabolism slows its rate to the point where another metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway a process called "metabolic switching".

Deuterium tracers, such as deuterium-labeled drugs and doses, in some cases repeatedly, of thousands of milligrams of deuterated water, are also used in healthy humans of all ages, including neonates and pregnant women, without reported incident (e.g. Pons G and Rey E, *Pediatrics* 1999 104: 633; Coward W A et al., *Lancet* 1979 7: 13; Schwarcz H P, *Control. Clin. Trials* 1984 5(4 Suppl): 573; Rodewald L E et al., *J. Pediatr.* 1989 114: 885; Butte N F et al. *Br. J. Nutr.* 1991 65: 3; MacLennan A H et al. *Am. J. Obstet Gynecol.* 1981 139: 948). Thus, it is clear that any deuterium released, for instance, during the metabolism of compounds of this invention poses no health risk.

The weight percentage of hydrogen in a mammal (approximately 9%) and natural abundance of deuterium (approximately 0.015%) indicates that a 70 kg human normally contains nearly a gram of deuterium. Furthermore, replacement of up to about 15% of normal hydrogen with deuterium has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, *Ann. N.Y. Acad. Sci.* 1960 84: 770; Thomson J F, *Ann. New York Acad. Sci.* 1960 84: 736; Czajka D M et al., *Am. J. Physiol.* 1961 201: 357). Higher deuterium concentrations, usually in excess of 20%, can be toxic in animals. However, acute replacement of as high as 15%-23% of the hydrogen

in humans' fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp. 125-134; Diabetes Metab. 23: 251 (1997)).

Increasing the amount of deuterium present in a compound above its natural abundance is called enrichment or deuterium-enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

The hydrogens present on a particular organic compound have different capacities for exchange with deuterium. Certain hydrogen atoms are easily exchangeable under physiological conditions and, if replaced by deuterium atoms, it is expected that they will readily exchange for protons after administration to a patient. Certain hydrogen atoms may be exchanged for deuterium atoms by the action of a deuterium acid such as D₂SO₄/D₂O. Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchangeable for deuterium atoms. However, deuterium atoms at the remaining positions may be incorporated by the use of deuterated starting materials or intermediates during the construction of compounds of the invention.

Deuterated and deuterium-enriched compounds of the invention can be prepared by using known methods described in the literature. Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Relevant procedures and intermediates are disclosed, for instance in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J et al., *J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; U.S. Pat. Nos. 7,538,189; 7,534,814; 7,531,685; 7,528,131; 7,521,421; 7,514,068; 7,511,013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; 20090082471, the methods are hereby incorporated by reference.

A further aspect of the present invention relates to a pharmaceutical composition comprising at least one compound of the general formula I and/or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof as detailed above, and a pharmaceutically acceptable carrier; or comprising at least one compound I wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, preferably wherein at least one hydrogen atom has been replaced by a deuterium atom, in combination with at least one pharmaceutically acceptable carrier and/or auxiliary substance. Suitable carriers depend inter alia on the dosage form of the composition and are known in principle to the skilled worker. Some suitable carriers are described hereinafter.

The present invention furthermore relates to a compound I as defined above or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof for use as a medicament. The present invention also relates to a compound I as defined above or an N-oxide, a stereoisomer or a pharmaceutically acceptable salt thereof for the treatment of

vasopressin-related diseases, especially of disorders which respond to the modulation of the vasopressin receptor and in particular of the V1b receptor.

A further aspect of the present invention relates to the use of compounds of the formula I and/or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasopressin-related diseases, especially of disorders which respond to the modulation of the vasopressin receptor and in particular of the V1b receptor.

Vasopressin-related diseases are those in which the progress of the disease is at least partly dependent on vasopressin, i.e. diseases which show an elevated vasopressin level which may contribute directly or indirectly to the pathological condition. In other words, vasopressin-related diseases are those which can be influenced by modulating the vasopressin receptor, for example by administration of a vasopressin receptor ligand (agonist, antagonist, partial antagonist/agonist, inverse agonist etc.).

Affective disorders have been related to excessive vasopressin function. Therefore, treatment with compounds targeting the vasopressin system, such as vasopressin antagonists are likely to benefit patients suffering from affective disorders (see for example Surget A., Belzung C., Involvement of vasopressin in affective disorders, *Eur. J. Pharm.* 2008, 583, 340-349). Affective disorders (mood disorders) include depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma and stressor-related disorders as well as bipolar and related disorders. V1b antagonist have been shown to have anti-drug abuse effects and reduce drug withdrawal effect (see e.g. Zhou Y., Leri F., Cummins E., Hoeschele M., Kreek M. J., Involvement of arginine vasopressin and V1b receptor in heroin withdrawal and heroin seeking precipitated by stress and by heroin. *Neuropsychopharmacology*, 2008, 33, 226-236). Therefore, compounds targeting the vasopressin system, such as vasopressin antagonists, are thought to be effective for treatment of substance-related and addictive disorders. V1b receptors play a role in a range of emotional responses such as aggression. Attenuating V1b receptor function genetically or with antagonist reduces aggressive behavior (Blanchard R. J., Griebel G., Farrokhi C., Markham C., Yang M., Blanchard D. C., AVP V1b selective antagonist SSR149415 blocks aggressive behaviors in hamsters. *Pharmacol. Biochem. Behav.* 2005, 80, 189-194; Wersinger S. R., Ginns E. I., O'Carroll A. M., Lolait S. J., Young W. S., III, Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. *Mol. Psychiatry*, 2002, 7, 975-984). Therefore, attenuating V1b antagonists functioning is likely to reduce aggression and agitation in disorders such as Alzheimer's disease and schizophrenia and other psychiatric and neurological disorders in which aggressive behavior occurs, such as Alzheimer's disease, schizophrenia, bipolar disorder, frontal lobe injuries or substance use disorders.

High cortisol levels have been correlated to reduced cognitive performance in elderly and AD (Alzheimer's disease) patients, and such correlations are more pronounced in subjects carrying the APOε4 allele, which is a risk factor for AD (see for example Lee B. K., Glass T. A., Wand G. S., McAtee M. J., Bandeen-Roche K., Bolla K. I., Schwartz B. S., Apolipoprotein e genotype, cortisol, and cognitive function in community-dwelling older adults. *Am. J. Psychiatry* 2008, 165, 1456-1464). Furthermore, increased plasma cortisol has been associated with more rapid disease progression in AD patients. Animal studies show an interaction between glucocorticoids and AD pathology, including amyloid precursor protein and tau accumulation (see for example

Budas G., Coughlan C. M., Seckl J. R., Breen K. C., The effect of corticosteroids on amyloid beta precursor protein/amyloid precursor-like protein expression and processing in vivo. *Neurosci. Lett.*, 1999, 276, 61-64). Cognitive performance can be impaired by stress or exposure to high doses of corticosterone in laboratory animals (for review see Roozendaal B., Systems mediating acute glucocorticoid effects on memory consolidation and retrieval. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2003, 27, 1213-1223). Therefore, lowering cortisol by treatment with V1b antagonist may enhance cognition or prevent/slow down the pathology or cognitive decline Alzheimer's disease patients and in patients with other cognitive impairment such as schizophrenia and depression.

In a preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from diabetes, insulin resistance, nocturnal enuresis, incontinence and diseases in which impairments of blood clotting occur, and/or for delaying micturition; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed diseases. The term "diabetes" means all types of diabetes, especially diabetes mellitus (including type I and especially type II), diabetes renalis and in particular diabetes insipidus. The types of diabetes are preferably diabetes mellitus of type II (with insulin resistance) or diabetes insipidus.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from hypertension, pulmonary hypertension, heart failure, myocardial infarction, coronary spasm, unstable angina, PTCA (percutaneous transluminal coronary angioplasty), ischemias of the heart, impairments of the renal system, edemas, renal vasospasm, necrosis of the renal cortex, hyponatremia, hypokalemia, Schwartz-Bartter syndrome, impairments of the gastrointestinal tract, gastric vasospasm, hepatocirrhosis, gastric and intestinal ulcers, emesis, emesis occurring during chemotherapy, and travel sickness; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed diseases.

The compounds of the invention of the formula I or their N-oxides, stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can also be used for the treatment of various vasopressin-related complaints which have central nervous causes or alterations in the HPA axis (hypothalamic pituitary adrenal axis), for example for affective disorders such as depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma and stressor-related disorders, and bipolar and related disorders. Depressive disorders include for example dysthymic disorders, major depression, seasonal depression, treatment-resistant depression disorders, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, or childhood onset mood disorders. Anxiety disorders include for example phobias, specific phobias, general anxiety disorders, panic disorders, drug withdrawal-induced anxiety disorders, separation anxiety disorder, selective mutism, social

anxiety disorder, agoraphobia, substance/medication-induced anxiety disorder and anxiety disorder due to another medical condition. Obsessive-compulsive and related disorders include for example obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder, substance/medication-induced obsessive-compulsive and related disorder and other specified obsessive-compulsive and related disorders. Trauma and stressor-related disorders include for example reactive attachment disorder, disinhibited social engagement disorder, post-traumatic stress disorder, acute stress disorder, adjustment disorder and other specified trauma- and stressor-related disorders. Bipolar and related disorders include for example bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition and unspecified bipolar and related disorder.

Vasopressin-related complaints which have central nervous causes or alterations in the HPA axis are further cognitive disorders such as Alzheimer's disease, MCI (Mild Cognitive Impairment) and CIAS (Cognitive Impairment Associated with Schizophrenia).

The compounds of the invention of the formula I and their N-oxides, a stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can likewise be employed for the treatment of anxiety disorders and stress-dependent anxiety disorders, such as, for example, generalized anxiety disorders, phobias, specific phobias, post-traumatic anxiety disorders, panic anxiety disorders, obsessive-compulsive anxiety disorders, acute stress-dependent anxiety disorders, drug withdrawal-induced anxiety disorders, separation anxiety disorder, selective mutism, social anxiety disorder, agoraphobia, substance/medication-induced anxiety disorder and anxiety disorder due to another medical condition and social phobia. The compounds of the invention of the formula I and their N-oxides, a stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can likewise be employed for the treatment of obsessive-compulsive and related disorders, including, for example, obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder, substance/medication-induced obsessive-compulsive and related disorder and other specified obsessive-compulsive and related disorders. The compounds of the invention of the formula I and their N-oxides, a stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can likewise be employed for the treatment of trauma and stressor-related disorders, including, for example, reactive attachment disorder, disinhibited social engagement disorder, post-traumatic stress disorder, acute stress disorder, adjustment disorder and other specified trauma- and stressor-related disorders.

The compounds of the invention of the formula I and their N-oxides, stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can likewise be employed for the treatment and/or prophylaxis of social impairment, such as autism or social impairment related with schizophrenia.

The compounds of the invention of the formula I and their N-oxides, stereoisomers or pharmaceutically acceptable salts or the pharmaceutical composition of the invention can likewise be employed for the treatment and/or prophylaxis of increased aggression in conditions selected from Alzheimer's disease, schizophrenia, bipolar disorder, frontal lobe injuries and substance use disorders.

The compounds of the invention can furthermore also be employed for the treatment of memory impairments, Alzheimer's disease, psychoses, psychotic disorders, sleep disorders and/or Cushing's syndrome, and all stress-dependent diseases.

Accordingly, a further preferred embodiment of the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of affective disorders; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of affective disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of anxiety disorders and/or stress-dependent anxiety disorders; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of the above-listed disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of memory impairments and/or Alzheimer's disease; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of the above-listed diseases.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of psychoses and/or psychotic disorders; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of the above-listed disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of Cushing's syndrome or other stress-dependent diseases; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of the above-listed diseases.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of sleep disorders; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of sleep disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of depressive disorders; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of depressive disorders. In the case of depressive disorders, specific mention is to be made of childhood onset mood

disorders, i.e. depressive moods having their onset in childhood, but also of major depression, seasonal depression, bipolar and related disorders, dysthymic disorders, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition, and especially of major depression and seasonal depression as well as of the depressive phases of bipolar disorders. Bipolar and related disorders include for example bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition and unspecified bipolar and related disorder. The invention also relates to compounds of the formula I or N-oxides, stereoisomers or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of treatment-resistant depression disorders and for the use in an add-on therapy of depressive disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of vasomotor symptoms and/or thermoregulatory dysfunctions such as, for example, the hot flush symptom; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment of the above-listed diseases.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of drug or pharmaceutical dependencies and/or dependencies mediated by other factors, for the treatment of drug-use disorders, for the treatment and/or prophylaxis of stress caused by withdrawal of one or more factors mediating the dependence and/or for the treatment and/or prophylaxis of stress-induced relapses into drug or pharmaceutical dependencies and/or dependencies mediated by other factors; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed diseases. To be more precise, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of substance-related and addictive disorders such as substance use disorder, substance-induced disorder, alcohol use disorder, alcohol intoxication, alcohol withdrawal, unspecified alcohol-related disorder, caffeine intoxication, caffeine withdrawal, unspecified caffeine disorder, cannabis use disorder, cannabis withdrawal, unspecified cannabis-related disorder, phencyclidine use disorder, other hallucinogen use disorders, phencyclidine intoxication, other hallucinogen disorders, hallucinogen persisting perception disorder, unspecified phencyclidine disorder, inhalant use disorder, inhalant intoxication, opioid use disorder, opioid withdrawal, sedative, hypnotic or anxiolytic use disorder, sedative, hypnotic or anxiolytic withdrawal, stimulant use disorder, stimulant intoxication, stimulant withdrawal, tobacco use disorder, tobacco withdrawal, unspecified tobacco-related disorder, other (or unknown) substance use disorders, other (or unknown) substance intoxication, other (or unknown) substance withdrawal, other (or unknown) substance related disorder and gambling disorder; as well as to compounds of

the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed diseases.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of schizophrenia and/or psychosis; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of pain, e.g. acute or chronic pain, preferably chronic pain, especially neuropathic pain; as well as to compounds of the invention of the formula I or of an N-oxide, a stereoisomer or of pharmaceutically acceptable salts thereof for the treatment and/or prophylaxis of the above-listed disorders. Chronic pain may be a complex regional pain syndrome, pain arising from peripheral neuropathies, post-operative pain, chronic fatigue syndrome pain, tension-type headache, pain arising from mechanical nerve injury and severe pain associated with diseases such as cancer, metabolic disease, neurotropic viral disease, neurotoxicity, inflammation, multiple sclerosis or any pain arising as a consequence of or associated with stress or depressive illness.

A further aspect of the invention relates to a compound I or pharmaceutically acceptable salts thereof for use as a medicament, and to a compound I or an N-oxide, a stereoisomer or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of the above-defined diseases.

A further aspect of the invention relates to a method for the treatment and/or prophylaxis of vasopressin-related diseases, in which an effective amount of at least one compound of the invention of the formula I or of an N-oxide, a stereoisomer or of at least one pharmaceutically acceptable salt thereof or of a pharmaceutical composition of the invention is administered to a patient in need thereof.

Concerning the definition of vasopressin-related diseases, reference is made to the above statements made in context with the use according to the invention. Thus, preferred embodiments of the method of the invention correspond to preferred embodiments of the use according to the invention.

The patient to be treated prophylactically or therapeutically with the method of the invention is preferably a mammal, for example a human or a nonhuman mammal or a nonhuman transgenic mammal. Specifically it is a human.

The compounds of the general formula I and their pharmaceutically acceptable salts as detailed above can be prepared by a skilled worker with knowledge of the technical teaching of the invention in implementing and/or in analogous implementation of process steps known per se.

The compounds I and/or their pharmaceutically acceptable salts, N-oxides and their stereoisomers are distinguished by having a selectivity for the vasopressin V1b receptor subtype vis-à-vis at least one of the closely related vasopressin/oxytocin receptor subtypes (for example vasopressin V1a, vasopressin V2 and/or oxytocin).

Alternatively, or preferably in addition, the compounds I and/or their pharmaceutically acceptable salts, N-oxides and a stereoisomers are distinguished by having an improved metabolic stability.

The metabolic stability of a compound can be measured for example by incubating a solution of this compound with liver microsomes from particular species (for example rat, dog or human) and determining the half-life of the compound under these conditions (R S Obach, *Curr Opin Drug Discov Devel.* 2001, 4, 36-44). It is possible in this connection to conclude from an observed longer half-life that the metabolic stability of the compound is improved. The stability in the presence of human liver microsomes is of particular interest because it makes it possible to predict the metabolic degradation of the compound in the human liver. Compounds with increased metabolic stability (measured in the liver microsome test) are therefore probably also degraded more slowly in the liver. The slower metabolic degradation in the liver may lead to higher and/or longer-lasting concentrations (active levels) of the compound in the body, so that the elimination half-life of the compounds of the invention is increased. Increased and/or longer-lasting active levels may lead to a better activity of the compound in the treatment or prophylaxis of various vasopressin-related diseases. In addition, an improved metabolic stability may lead to an increased bioavailability after oral administration, because the compound is subject, after absorption in the intestine, to less metabolic degradation in the liver (so-called first pass effect). An increased oral bioavailability may, owing to an increased concentration (active level) of the compound, lead to a better activity of the compound after oral administration.

The compounds of the invention are effective after administration by various routes. Possible examples are intravenous, intramuscular, subcutaneous, topical, intratracheal, intranasal, transdermal, vaginal, rectal, sublingual, buccal or oral administration, and administration is frequently intravenous, intramuscular or, in particular, oral.

The present invention also relates to pharmaceutical compositions which comprise an effective dose of a compound I of the invention and/or an N-oxide, a stereoisomer and/or a pharmaceutically acceptable salt thereof and suitable pharmaceutical carriers (drug carriers).

These drug carriers are chosen according to the pharmaceutical form and the desired mode of administration and are known in principle to the skilled worker.

The compounds of the invention of the formula I, their N-oxides, stereoisomers or optionally suitable salts of these compounds can be used to produce pharmaceutical compositions for oral, sublingual, buccal, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal, vaginal or rectal administration, and be administered to animals or humans in uniform administration forms, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases.

The suitable administration forms (dose units) include forms for oral administration such as tablets, gelatin capsules, powders, granules and solutions or suspensions for oral intake, forms for sublingual, buccal, intratracheal or intranasal administration, aerosols, implants, forms of subcutaneous, intramuscular or intravenous administration and forms of rectal administration.

The compounds of the invention can be used in creams, ointments or lotions for topical administration.

In order to achieve the desired prophylactic or therapeutic effect, the dose of the active ingredient can vary between 0.01 and 50 mg per kg of body weight and per day.

Each unit dose may comprise from 0.05 to 5000 mg, preferably 1 to 1000 mg, of the active ingredient in combination with a pharmaceutical carrier. This unit dose can be administered once to 5 times a day, so that a daily dose of from 0.5 to 25 000 mg, preferably 1 to 5000 mg, is administered.

If a solid composition is prepared in the form of tablets, the active ingredient is mixed with a solid pharmaceutical carrier such as gelatin, starch, lactose, magnesium stearate, talc, silicon dioxide or the like.

The tablets can be coated with sucrose, a cellulose derivative or another suitable substance or be treated otherwise in order to display a sustained or delayed activity and to release a predetermined amount of the active ingredient continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with an extender and including the resulting mixture in soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops may contain active ingredients together with a sweetener, which is preferably calorie-free, methylparaben or propylparaben as antiseptics, a flavoring and a suitable coloring substance.

Water-dispersible powders or granules may comprise the active ingredients mixed with dispersants, wetting agents or suspending agents, such as polyvinylpyrrolidones, and sweeteners or masking flavors.

Rectal or vaginal administration is achieved by using suppositories which are prepared with binders which melt at rectal temperature, for example cocoa butter or polyethylene glycols. Parenteral administration is effected by using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which comprise pharmacologically acceptable dispersants and/or wetting agents, for example propylene glycol or polyethylene glycol.

The active ingredient may also be formulated as microcapsules or centrosomes, if suitable with one or more carriers or additives.

The compositions of the invention may, in addition to the compounds of the invention, comprise other active ingredients which may be beneficial for the treatment of the disorders or diseases indicated above.

The present invention thus further relates to pharmaceutical compositions in which a plurality of active ingredients are present together, where at least one of these is a compound I of the invention, or salt thereof.

The invention is explained in more detail below by means of examples, but the examples are not to be understood to be restrictive.

The compounds of the invention can be prepared by various synthetic routes. The methods mentioned, as described accordingly in synthesis schemes 1 to 4, are explained in greater detail merely by way of example using the given examples without being exclusively restricted to synthesis routes 1 to 4 or analogous methods.

EXPERIMENTAL SECTION

Abbreviations used:

rt room temperature (20-25° C.)

h hour(s)

min minute(s)

d day(s)

quant. quantitative

eq. equivalents

conc. concentrated

TLC thin layer chromatography

RP reversed phase

aq. aqueous

MeOH methanol

EtOH ethanol

5 THF: tetrahydrofuran

DMF dimethylformamide

DMSO: dimethyl sulfoxide

EtOAc ethyl acetate

TFA: trifluoroacetic acid

10 DIPEA diisopropylethyl amine

p: pseudo (for example pt pseudo triplet)

b: broad (for example bs broad singlet)

s: singlet

d: doublet

t: triplet

15 m: multiplet

dd: doublet of doublets

dt: doublet of triplets

tt: triplet of triplets

20 I. Preparation of Compounds of Formula I

Example 1

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} and R^{8c} are H and R^{8b} is methoxy)

1.1 (S)-Phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl) carbamate

35 The title compound was prepared as described in WO2009/071691.

ESI-MS: [M+K⁺]=623.2; [M+Na⁺]=608.2; [M+H⁺]=585.2

1.2 (S)-tert-Butyl 6-((5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamoyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

45 DIPEA (2.05 mmol, 0.36 ml) was added to a suspension of tert-butyl 2,6-diazaspiro[3.3]-heptane-2-carboxylate oxalate (0.41 mmol, 118 mg) in CH₂Cl₂ (10 ml). Once in solution, (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamate (0.41 mmol, 240 mg) was added and the mixture was stirred for 12 h. The mixture was poured into cold 5% aq. K₂CO₃ (10 ml) and extracted with CH₂Cl₂ (3×10 ml); and the organic phases were combined, washed with water (3×10 ml), dried on Na₂SO₄, filtered, evaporated, and finally passed through a silicagel column (eluent: EtOAc). Yield: 205.5 mg (73%).

ESI-MS: [M⁺-55 (isobutene)]=633.2; [M+H⁺]=689.2

60 1.3 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

65 TFA (20 eq., 5.95 mmol, 0.46 ml) was added to a solution of (S)-tert-butyl 6-((5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamoyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (0.30 mmol,

151

205 mg) in CH₂Cl₂ (10 ml). The mixture was stirred at rt for 1 h, poured into cold 5% aq. K₂CO₃ (10 ml) and extracted with CH₂Cl₂ (3×10 ml). The organic phases were combined, washed with water (3×10 ml), dried on Na₂SO₄, filtered, evaporated and finally passed through a silicagel column (eluent: CH₂Cl₂:2M NH₃/EtOH 17:3). Yield: 52.7 mg (30%).

ESI-MS: [M+H⁺]=589.3

1.4 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxo-indolin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide (0.04 mmol, 25 mg), 2-morpholinoacetaldehyde (NaHSO₃-salt, 0.04 mmol, 10 mg), sodium acetate (0.09 mmol, 7 mg) and acetic acid (conc., 0.09 mmol, 5 mg) were dissolved in EtOH (1.5 ml) and stirred for 1 h. NaCNBH₃ (0.05 mmol, 3.2 mg) was added portionwise and stirred at rt for 12 h. The mixture was poured into cold 5% aq. K₂CO₃ (5 ml) and extracted with ethyl acetate (3×5 ml); the organic phases were combined, washed with water (3×5 ml) and dried on Na₂SO₄, filtered, evaporated and finally passed through a silicagel column (eluent: CH₂Cl₂:2M NH₃/EtOH 19:1). Solvents were evaporated, the residue precipitated in water and the filtrate evaporated in vacuo. Yield: 4.81 mg (16%).

ESI-MS: [M+H⁺]=702.3

The product was obtained in form of two conformers. These conformers were separated via RP-HPLC with following column: LUNA C18 Axia 100A 5μ 75×30; flow 40 ml/min; eluent gradient H₂O/10-90% methanol+0.1% trifluoroacetic acid.

Conformer 1A of N-[(3S)-5-cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

ESI-MS: [M+H⁺]=702.2

¹H NMR (CDCl₃, 600 MHz): d=8.22 (d, 1H), 7.85-7.78 (m, 2H), 7.78-7.72 (m, 2H), 7.37 (s br, 1H), 7.00 (s br, 1H), 6.94-6.85 (m br, 4H incl. 6.89 d), 4.41 (m sym., 2H), 4.35-4.30 (m, 2H), 4.30-4.22 (m, 3H), 4.17-4.03 (m br, 2H), 3.94-3.84 (m, 7H incl. 3.87 s), 3.71 (br. s., 1H), 3.54-3.45 (m, 2H incl. 3.50 s), 3.16 (s br., 2H), 3.04 (br. s., 4H), 1.23 (m sym., 4H)

Conformer 1B of N-[(3S)-5-cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

ESI-MS: [M+H⁺]=702.2

¹H NMR (CDCl₃, 600 MHz): d=8.13 (d, 1H), 8.05 (d, 2H), 8.00 (d, 1H), 7.64 (s, 1H), 7.61 (d, 1H), 6.99 (d, 2H), 6.85 (m sym., 1H), 6.44 (s, 1H), 4.52 (m sym., 2H), 4.26 (dd, 4H), 4.06 (s br., 4H), 3.94 (m, 4H), 3.88 (s, 3H), 3.59 (m sym., 2H), 3.24 (m sym., 2H), 3.10 (br. s., 4H), 1.46 (t, 3H).

152

The following compounds were prepared analogously:

Example 2

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(3-morpholinopropyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 3-(morpholin-4-yl)-n-propyl, R^{8a} and R^{8c} are H and R^{8b} is methoxy)

ESI-MS: [M+H⁺]=716.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 2A: retention time: 1.38 min

Conformer 2B: retention time: 1.46 min

Example 3

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluoro-2-methoxy-phenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is F and R^{8c} is H)

ESI-MS: [M+H⁺]=720.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 3A: retention time: 1.52 min

Conformer 3B: retention time: 1.61 min

Example 4

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-[(5-methoxy-2-pyridyl)sulfonyl]-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.65, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=703.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 4A: retention time: 1.48 min

Conformer 4B: retention time: 1.55 min

Example 5

N-[(3S)-5-cyano-1-(4-cyanophenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is CN and R^{8c} is H)

ESI-MS: [M+H⁺]=697.3

153

Example 6

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(2-fluoro-4-methoxy-phenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is F, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=720.2

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 6A: retention time: 1.54 min

Conformer 6B: retention time: 1.66 min

Example 7

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=732.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 7A: retention time: 3.99 min

Conformer 7B: retention time: 4.60 min

Example 8

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

ESI-MS: [M+H⁺]=690.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 8A: retention time: 3.78 min

Conformer 8B: retention time: 4.89 min

Example 9

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-diethylaminoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(diethylamino)-ethyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

154

9.1 N,N-Diethyl-2-(2,6-diazaspiro[3.3]heptan-2-yl)ethanamine tris(2,2,2-trifluoroacetate)

tert-Butyl 6-(2-(diethylamino)ethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate was deprotected with TFA as described in step 1.3 of example 1. The product was further reacted immediately in order to avoid degradation.

9.2 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-diethylaminoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S)-Phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamate and N,N-diethyl-2-(2,6-diazaspiro[3.3]heptan-2-yl)ethanamine tris(2,2,2-trifluoroacetate) were reacted as described in step 1.2 of example 1.

ESI-MS: [M+Na⁺]=710.5; [M+H⁺]=688.3;

Example 10

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

ESI-MS: [M+H⁺]=686.2

Example 11

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is H and R^{8c} is H)

ESI-MS: [M+H⁺]=702.3

Example 12

N-[(3S)-5-Cyano-1-(4-methoxyphenyl)sulfonyl-3-(2-methoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.17, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

The title compound was prepared from (S)-phenyl (5-cyano-1-((4-methoxyphenyl)sulfonyl)-3-(2-methoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate as described in step 1.2 of example 1.

ESI-MS: [M+H⁺]=688.2

155

Example 13

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[2-(1-piperidyl)ethyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(piperidin-1-yl)-ethyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

13.1 2-(2-(Piperidin-1-yl)ethyl)-2,6-diazaspiro[3.3]heptane tris(2,2,2-trifluoroacetate)

The title compounds was prepared from tert-butyl 6-(2-(piperidin-1-yl)ethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate as described in step 9.1 of example 9.

13.2 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-(piperidin-1-yl)ethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

The title compounds was prepared from (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate and 2-(2-(piperidin-1-yl)ethyl)-2,6-diazaspiro[3.3]heptane tris(2,2,2-trifluoroacetate) as described in step 1.2 of example 1.

ESI-MS: [M+H⁺]=544.3

13.3 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[2-(1-piperidyl)ethyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide

Potassium tert-butanolate (0.08 mmol, 8 mg) was added to a solution of (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-(piperidin-1-yl)ethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 13.2 (0.06 mmol, 33 mg) in THF (1.5 ml) cooled down to 0° C.; and the mixture was further stirred for 1 h at 0° C. Then 4-methoxybenzene-1-sulfonyl chloride (0.07 mmol, 14 mg) was added and stirred for 12 h. The mixture was poured into cold 5% aq. K₂CO₃ (5 ml) and extracted with CH₂Cl₂ (3×5 ml). The organic phases were combined, washed with water (3×5 ml), dried on Na₂SO₄, filtered, evaporated, and finally passed through a silicagel column (eluent: CH₂Cl₂:MeOH 9:1). Yield: 11 mg (25%).

ESI-MS: [M+H⁺]=700.3

The product was obtained in form of two conformers. These conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 13A: retention time: 1.47 min

Conformer 13B: retention time: 1.57 min

In examples 14 to 18 only one conformer was observed.

Example 14

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is H and R^{8c} is H)

156

14.1 tert-Butyl 6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

K₂CO₃ (52.0 mmol, 7.2 g) was added to a suspension of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate oxalate (10.4 mmol, 3.0 g) in DMF (90 ml). After 1 h stirring at rt, 4-(2-bromoethyl)morpholine hydrochloride (11.5 mmol, 2.6 g) was added portionwise and the mixture was stirred at rt for 12 h. The precipitate was filtered off, and the filtrate evaporated in vacuo. The residue was passed through a silicagel column (eluent: CH₂Cl₂:MeOH 9:1). Yield: 1.9 g (59%).

14.2 4-(2-(2,6-Diazaspiro[3.3]heptan-2-yl)ethyl)morpholine tris(2,2,2-trifluoroacetate)

TFA (61 mmol, 4.7 ml) was added to a solution of tert-butyl 6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate from step 14.1 (6.1 mmol, 1.9 g) in CH₂Cl₂ (15 ml). The mixture was stirred at rt for 1 h, and solvents were removed under vacuo. The residue was crystallized by addition of a few drops of diethyl ether to the solution in MeOH. Yield: 2.2 g (65%).

14.3 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

DIPEA (21.7 mmol, 3.8 ml) was added to a suspension of 4-(2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl)morpholine tris(2,2,2-trifluoroacetate) from step 14.2 (4.3 mmol, 2.4 g) in CH₂Cl₂ (50 ml). Once in solution, (S)-phenyl(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate (4.3 mmol, 1.8 g) was added and the mixture was further stirred for 12 h. The mixture was then poured into cold 5% aq. K₂CO₃ (50 ml) and extracted with CH₂Cl₂ (3×50 ml). The organic phases were combined, washed with water (3×50 ml), dried on Na₂SO₄, filtered and evaporated. The residue was precipitated in ether, filtered off, washed with ether, and dried in vacuo.

Yield: 2.13 g (92%).

ESI-MS: [M+H⁺]=532.2

14.4 N-[(3S)-5-cyano-3-(2-ethoxy-3-pyridyl)-1-(2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

The title compound was obtained in analogy to example 13 from (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 14.3 and 2-methoxybenzene-1-sulfonyl chloride.

ESI-MS: [M+H⁺]=702.3 (only 1 conformer observed)

Example 15

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

The title compound was obtained in analogy to example 13 from (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

157

dolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 14.3 and 2,4-dimethoxybenzene-1-sulfonyl chloride.

ESI-MS: $[M+H^+]=732.3$ (only 1 conformer observed)

Example 16

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X^1 is NH, R^1 is CN, R^2 is H, R^5 is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

The title compound was obtained in analogy to example 13 from (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 14.3 and 4-methylbenzene-1-sulfonyl chloride.

ESI-MS: $[M+H^+]=686.3$ (1 conformer)

Example 17

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluoro-2-methoxy-phenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X^1 is NH, R^1 is CN, R^2 is H, R^5 is 2-(morpholin-4-yl)-ethyl, R^{8a} is methoxy, R^{8b} is F and R^{8c} is H)

The title compound was obtained in analogy to example 13 from (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 14.3 and 4-fluoro-2-methoxybenzene-1-sulfonyl chloride.

ESI-MS: $[M+H^+]=720.3$ (only 1 conformer observed)

Example 18

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(2-fluoro-4-methoxy-phenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X^1 is NH, R^1 is CN, R^2 is H, R^5 is 2-(morpholin-4-yl)-ethyl, R^{8a} is F, R^{8b} is methoxy and R^{8c} is H)

The title compound was obtained in analogy to example 13 from (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 14.3 and 2-fluoro-4-methoxybenzene-1-sulfonyl chloride.

ESI-MS: $[M+H^+]=720.3$ (only 1 conformer observed)

Example 19

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-6-fluoro-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X^1 is NH, R^1 is CN, R^2 is F, R^5 is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

158

19.1 (S)-Phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-6-fluoro-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamate

5 Pyridine (1.5 mmol, 0.1 ml) was added to a solution of (S)-3-amino-3-(2-ethoxypyridin-3-yl)-6-fluoro-1-((4-methoxyphenyl)sulfonyl)-2-oxoindoline-5-carbonitrile (described in WO2009/071690, 0.15 mmol, 72 mg) in CH_2Cl_2 (5 ml) cooled at 5° C. Phenyl chloroformate (0.16 mmol, 26 mg) was added dropwise and the mixture stirred for 1 h at 0° C. The reaction was monitored by TLC (eluted with MeOH (5%)/ CH_2Cl_2). The mixture was poured into cold water (5 ml) and extracted with CH_2Cl_2 (3×5 ml). The combined organic phases were washed with water (3×5 ml), dried on Na_2SO_4 , filtered and evaporated in vacuo. The residue was used in the next step without further purification.

20 19.2 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-6-fluoro-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

25 The title compound was obtained in analogy to step 1.2 of example 1 from (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-6-fluoro-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamate from step 19.2 and 4-(2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl)morpholine tris(2,2,2-trifluoroacetate) (see step 14.2 of example 14; 0.1 mmol, 65 mg).

ESI-MS: $[M+H^+]=720.30$

Example 20

35 3-(2-Ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-3-[2-[2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptan-6-yl]-2-oxo-ethyl]-2-oxo-indoline-5-carbonitrile

45 (Compound of formula I.1, wherein X^1 is CH_2 , R^1 is CN, R^2 is H, R^5 is 2-(morpholin-4-yl)-ethyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

DIPEA (0.9 mmol, 121 mg) was added to a solution of (2-(5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)acetic acid (synthesis described in WO2009/071687, 0.1 mmol, 68 mg) and 4-(2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl)-morpholine tris(2,2,2-trifluoroacetate) (see step 14.2 of example 14, 0.2 mmol, 89 mg) in CH_2Cl_2 (20 ml). Then 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (HATU, 0.3 mmol, 127 mg) was added and the mixture stirred at room temperature for 12 h. The reaction was monitored by TLC (eluted with MeOH (5%)/ CH_2Cl_2). The reaction mixture was diluted with CH_2Cl_2 and washed with water (20 mL each). The organic phase was dried on Na_2SO_4 , filtered and evaporated. It was passed through a silicagel column (eluent: MeOH (2%)/ CH_2Cl_2). Yield: 55 mg (59%).

ESI-MS: $[M+K^+]=739.20$; $[M+Na^+]=723.25$; $[M+H^+]=701.20$

65 The two enantiomers 20A and 20B were separated by chiral HPLC from the racemic title compound on following

159

column: DAICEL Chiralpak IC 2×25 cm; flow 12 ml/min; eluent n-heptane/ethanol/triethylamine 300:700:1.

Example 21

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethoxy)-6-azaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.2, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2-(morpholin-4-yl)-ethoxy, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

21.1 tert-Butyl 6-(2-morpholinoethoxy)-2-azaspiro[3.3]heptane-2-carboxylate

Potassium tert-butanolate (1.7 mmol, 188 mg) was added portionwise to a solution of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (1.5 mmol, 325 mg) in DMF abs. (2 ml) cooled at 0° C. After stirring for 1 h at 0° C., 4-(2-bromoethyl)morpholine hydrobromide (0.7 mmol, 199 mg) was added and the mixture was stirred for 12 h at rt. It was poured onto cold NaHCO₃ conc. (5 ml) and extracted with ether (3×5 ml). The organic phases were combined and washed once with NaHCO₃ conc. (5 ml) and dried on Na₂SO₄, filtered and evaporated. The residue was passed through a silicagel column (eluent: 1.) neat EtOAc; 2.) EtOAc:MeOH 1:1). Yield: 67.5 mg (27%).

21.2 4-(2-(2-Azaspiro[3.3]heptan-6-yloxy)ethyl)morpholine bis(2,2,2-trifluoroacetate)

tert-Butyl 6-(2-morpholinoethoxy)-2-azaspiro[3.3]heptane-2-carboxylate from step 21.1 (0.2 mmol, 66 mg) was deprotected with TFA (10 eq., 20 mmol, 231 mg) in CH₂Cl₂ (5 ml) at rt for 1 h. The product was used in the next step without further purification. Yield: 92 mg (quant).

21.3 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethoxy)-6-azaspiro[3.3]heptane-6-carboxamide

The title compound was prepared in analogy to step 1.2 of example 1 from (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-(4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamate and 4-(2-(2-azaspiro[3.3]heptan-6-yloxy)ethyl)morpholine bis(2,2,2-trifluoroacetate).

The filtrate was passed through a silicagel column (eluent: EtOAc:MeOH 17:3), which afforded two conformers of the title compound. Yield: Conformer 21A: 38 mg, 27%; conformer 21B: 28 mg, 20% (85% purity).

ESI-MS: [M+H⁺]=717.40

These two conformers were identified via HPLC (Column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: Acetonitrile/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.):

Conformer 21A: retention time: 1.39 min

Conformer 21B: retention time: 1.25 min

Example 22

(±)-N-[5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(Compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

160

Zinc(II) chloride (0.01 mmol, 1.5 mg) was added to a solution of (±)-N-(5-cyano-1-((2,4-dimethoxyphenyl)sulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate (0.02 mmol, 15 mg) and propan-2-one (0.03 mmol, 1.6 mg) in methanol (5 ml). The solution was stirred for 30 min at rt. Sodium cyanotrihydroborate (0.02 mmol, 1.4 mg) was added and the whole mixture was stirred for 2 d at rt. The reaction was monitored by TLC (eluent: 5% MeOH/CH₂Cl₂). The mixture was poured onto cold 5% aq. K₂CO₃ (30 mL) and extracted three times with 20 mL ethyl acetate. The combined organic phases were washed with water (3×20 mL), dried on Na₂SO₄, filtered and evaporated. The crude was purified using preparative TLC (eluent: 10% MeOH/CH₂Cl₂). Yield: 5 mg (37%).

ESI-MS: [M+H⁺]=744.30

Example 23

(±)-N-[5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(Compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylpiperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

23.1 tert-Butyl 6-(1-methylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

Acetic acid (10.4 mmol, 0.6 ml) and sodium triacetoxyhydroborate (10.4 mmol, 2.2 g, portionwise) were added to tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate oxalate (1.04 mmol, 300 mg) dissolved in THF (45 ml) under N₂. The mixture was stirred overnight, poured onto 5% K₂CO₃ aq. (50 ml), then extracted with EtOAc (3×50 ml), and chloroform (3×50 ml). The organic phases were combined, dried on Na₂SO₄, filtrated and concentrated in vacuo. The product was passed through a silicagel column (eluent: EtOAc:MeOH: 25% NH₃ aq. 15:3:2). Yield: 123 mg (40%).

23.2 2-(1-Methylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane trihydrochloride

tert-Butyl 6-(1-methylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate from step 23.1 (0.42 mmol, 123 mg) was dissolved in HCl (2M in diethylether, 10 ml). The reaction mixture was stirred at rt for 12 h. The precipitate was filtrated, taken up in MeOH and evaporated. Yield: 75.1 mg (92%).

23.3 (±)-Phenyl (5-cyano-1-((2,4-dimethoxyphenyl)sulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate

Phenyl chloroformate (1.3 eq., 2 mmol, 309 mg) was added dropwise over 10 min to a solution of 3-amino-1-(2,4-dimethoxyphenyl)sulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindoline-5-carbonitrile (1.5 mmol, 750 mg) and pyridine (15.2 mmol, 1.2 g) in CH₂Cl₂ (100 ml) cooled at 5° C. The mixture was allowed to warm up to room temperature and stirred for 12 h. 2 additional eq. of phenyl chloroformate (3 mmol, 475 mg) were added and the mixture was further stirred for 5 h at room temperature. The reaction was monitored by TLC eluted with 5% MeOH/CH₂Cl₂. The mixture was diluted with CH₂Cl₂ (50 ml) and water was

161

added (100 ml). The phases were separated and the organic layer was washed with sat. aq. Na₂CO₃ and water (1×200 ml), dried on Na₂SO₄, filtered and evaporated. The crude product was taken up into a small amount of CH₂Cl₂ and treated with diisopropyl ether. The mixture was stirred for 2 h and the precipitate filtered off and dried in vacuo (30° C.). Yield: 920 mg (quant.) ESI-MS: [M+K⁺]=653.00; [M+Na⁺]=637.10; [M+H⁺]=615.10

23.4 (±)-N-[5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

Triethylamine (0.13 mmol, 13 mg) was added to a solution of 2-(1-methylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane trihydrochloride from step 23.2 (0.04 mmol, 11 mg) and (±)-phenyl (5-cyano-1-(2,4-dimethoxyphenyl)sulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate from step 23.3 (0.02 mmol, 10 mg) in THF (1.5 ml). The mixture was stirred at room temperature for 12 h, poured onto cold 5% aq. K₂CO₃ and extracted three times with ethyl acetate (2 ml). The organic phases were combined and washed with water (3×2 ml), dried on Na₂SO₄, filtered and evaporated. The residue was purified by preparative TLC (eluent: 17:3 CH₂Cl₂/2M NH₃ in EtOH). Yield: 3.91 mg (34%).

ESI-MS: [M+H⁺]=716.30 (ca 90% purity)

Example 24

N-[(3S)-5-cyano-1-(4-cyanophenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is cyano and R^{8c} is H)

24.1 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(1-isopropylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

DIPEA (2.4 mmol, 0.4 ml) was added to a suspension of 2-(1-isopropylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane tris(2,2,2-trifluoroacetate) (0.48 mmol, 273 mg) in CH₂Cl₂ (10 ml). Once solved, (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamate (0.48 mmol, 200 mg) was added and the mixture was stirred for 12 h. The mixture was poured onto cold 5% aq. K₂CO₃ (10 ml) and extracted with CH₂Cl₂ (3×10 ml). The organic phases were combined, washed with water (3×10 ml) and dried with Na₂SO₄, filtered and evaporated. The residue was passed through a silicagel column (eluent: CH₂Cl₂:2M NH₃/EtOH 1:1). Yield: 127.4 mg (49%).

24.2 N-[(3S)-5-cyano-1-(4-cyanophenyl)sulfonyl-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

Potassium tert-butanolate (0.06 mmol, 6 mg) was added to (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(1-isopropylpiperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide from step 24.1 (0.06 mmol, 30 mg) dissolved in THF (1 ml) at 0° C. After 1 h stirring at 0° C., 4-cyanobenzene-1-sulfonyl chloride (0.06 mmol, 11 mg)

162

was added and the mixture stirred for 2 d at rt. The mixture was poured onto cold 5% aq. K₂CO₃ (5 ml) and extracted with EtOAc (3×5 ml). The organic phases were combined, washed with water (3×5 ml), dried on Na₂SO₄, filtered and evaporated. The residue was passed on a silicagel column (eluent: CH₂Cl₂:2M NH₃/EtOH 17:3). Yield: 12.12 mg (31%).

ESI-MS: [M+H⁺]=709.30 (ca 90% purity)

Example 25

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

The title compound was prepared in analogy to example 24 using 4-methylbenzene-1-sulfonyl chloride.

ESI-MS: [M+H⁺]=698.30

Example 26

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is oxetan-3-yl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

26.1 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide

The title compound was prepared in analogy to example 24.1 using 2-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane bis(2,2,2-trifluoroacetate).

ESI-MS: [M+H⁺]=475.20

26.2 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

The title compound was prepared in analogy to example 24.2 using (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide and 4-methylbenzene-1-sulfonyl chloride.

ESI-MS: [M+H⁺]=629.30

Example 27

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

ESI-MS: [M+H⁺]=702.30 (90% purity)

163

Example 28

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is oxetan-3-yl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

28.1 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate

(S)-tert-Butyl 6-((5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamoyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (0.1 mmol, 58 mg) was deprotected with TFA (20 eq., 2.2 mmol, 255 mg) in CH₂Cl₂ (10 ml). Yield: 56.3 mg (95%)

ESI-MS: [M+H⁺]=419, 20

28.2 (S)-tert-Butyl 4-(6-((5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamoyl)-2,6-diazaspiro[3.3]heptan-2-yl)piperidine-1-carboxylate

(S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate from step 28.1 (0.09 mmol, 50 mg), tert-butyl 4-oxopiperidine-1-carboxylate (0.09 mmol, 19 mg), sodium acetate (0.09 mmol, 8 mg) and conc. acetic acid (2 eq., 0.19 mmol, 11 μl) were dissolved in EtOH (5 ml) and stirred for 1 h. Sodium cyanotrihydroborate (0.11 mmol, 7 mg) was added portionswise and the mixture was stirred for 12 h at rt. The mixture was poured onto cold 5% aq. K₂CO₃ (5 ml) and extracted with ethyl acetate (3×5 ml). The organic phases were combined, washed with water (3×5 ml) and dried on Na₂SO₄, filtered and evaporated. Yield: 51.2 mg (91%).

ESI-MS: [M+H⁺]=602.30

28.3 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide bis(2,2,2-trifluoroacetate)

(S)-tert-Butyl 4-(6-((5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)carbamoyl)-2,6-diazaspiro[3.3]heptan-2-yl)piperidine-1-carboxylate from step 28.2 (0.08 mmol, 50 mg) was deprotected with TFA (20 eq., 1.7 mmol, 190 mg) in CH₂Cl₂ (5 ml). Yield: 59.8 mg (quant.)

ESI-MS: [M+H⁺]=502.30

28.4 (S)-N-(5-Cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(1-(oxetan-3-yl)piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide(R-2630)

(S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide bis(2,2,2-trifluoroacetate) from step 28.3 (0.08 mmol, 58 mg), oxetan-3-one (0.08 mmol, 6 mg), sodium acetate (0.16 mmol, 13 mg) and conc. acetic acid were dissolved in EtOH (1.5 ml). The mixture was stirred for 1 h and sodium cyanotrihydroborate (0.1 mmol, 6 mg) was added portionswise, and further stirred for 12 h at rt. The

164

mixture was poured onto cold 5% aq. K₂CO₃ (5 ml) and extracted with ethyl acetate (3×5 ml). The organic phases were combined, washed with water (3×5 ml), dried with Na₂SO₄, filtered and evaporated. Yield: 34.2 mg (77%).

ESI-MS: [M+H⁺]=558.30

28.5 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide

The title compound was prepared in analogy to example 24.2 using (S)-N-(5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(1-(oxetan-3-yl)piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide and 4-fluorobenzene-1-sulfonyl chloride.

ESI-MS: [M+H⁺]=716.30

Example 29

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=714.30

Example 30

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-(oxetan-3-yl)-piperidin-4-yl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

ESI-MS: [M+H⁺]=712.30 (90% purity)

Example 31

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(oxetan-3-yl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is oxetan-3-yl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

ESI-MS: [M+H⁺]=633.20

Example 32

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylpiperidin-4-yl, R^{8a} is methoxy, R^{8b} is H and R^{8c} is H)

The title compound was prepared in analogy to step 24.1 of example 24 using (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-((2-methoxyphenyl)sulfonyl)-2-oxo-indolin-3-yl)carbamate; ESI-MS: [M+H⁺]=686.20

165

The product was obtained in form of two conformers. These conformers were identified with following column: Grace, GROM_SIL 80 ODS 7 pH, 4 μ m, 40 \times 2 mm ID, System: Methanol/TFA, Flow: 0.6 ml/min, Inj. Vol: 3 μ l Temp: 65° C.

Conformer 32A: retention time: 4.78 min

Conformer 32B: retention time: 4.55 min

The conformers were separated via preparative HPLC with following column: xTerra prepMS C18 19 \times 150 mm 5 μ m; flow 15 ml/min; eluent gradient H₂O/10-100% MeOH+ 0.1% TFA

Conformer 32A: ESI-MS: [M+H⁺]=686.20

Conformer 32B: ESI-MS: [M+H⁺]=686.20

Example 33

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylpiperidin-4-yl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

The title compound was prepared in analogy to step 24.1 of example 24 using (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxo-indolin-3-yl)carbamate; ESI-MS: [M+H⁺]=686.30

The product was obtained in form of two conformers. These conformers were identified with following column: Grace, GROM_SIL 80 ODS 7 pH, 4 μ m, 40 \times 2 mm ID, System: Methanol/TFA, Flow: 0.6 ml/min, Inj. Vol: 3 μ l Temp: 65° C.

Conformer 33A: retention time: 4.90 min

Conformer 33B: retention time: 4.64 min

The conformers were separated via preparative HPLC with following column: xTerra prepMS C18 19 \times 150 mm 5 μ m; flow 15 ml/min; eluent gradient H₂O/10-100% MeOH+ 0.1% TFA

Conformer 33A: ESI-MS: [M+H⁺]=686.30

Conformer 33B: ESI-MS: [M+H⁺]=686.30

Example 34

N-[(3S)-1-(Benzenesulfonyl)-5-cyano-3-(2-ethoxy-3-pyridyl)-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylpiperidin-4-yl, R^{8a} is H, R^{8b} is H and R^{8c} is H)

The title compound was prepared in analogy to step 24.1 of example 24 using (S)-phenyl (5-cyano-3-(2-ethoxypyridin-3-yl)-2-oxo-1-(phenylsulfonyl)indolin-3-yl)carbamate.

ESI-MS: [M+H⁺]=656.20

The product was obtained in form of two conformers. These conformers were identified with following column: Macherey & Nagel Nucleosil C18 PPN, 100 \times 2.1, System: Methanol/TFA, Flow: 0.2 ml/min, Inj. Vol: 41 μ l Temp: 40° C.

Conformer 34A: retention time: 17.79 min

Conformer 34B: retention time: 19.74 min

The conformers were separated via preparative HPLC with following column: xTerra prepMS C18 19 \times 150 mm 5 μ m; flow 15 ml/min; eluent gradient H₂O/10-100% MeOH+ 0.1% TFA

Conformer 34A: ESI-MS: [M+H⁺]=656.20

Conformer 34B: ESI-MS: [M+H⁺]=656.20

166

Example 35

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-(oxetan-3-yl)-piperidin-4-yl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=727.30

The product was obtained in form of two conformers. These conformers were identified with following column: Zorbax Extended C18, 50 \times 2.1 mm ID, 1.8 μ m, System: ACN/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μ l Temp: 65° C.

Conformer 35A: retention time: 1.48 min

Conformer 35B: retention time: 1.83 min

The conformers were separated via preparative RP-HPLC with following column: LUNA C18 Axia 100A 5 μ 75 \times 30; flow 40 ml/min; eluent gradient H₂O/10-90% MeOH+0.1% TFA

Conformer 35A: ESI-MS: [M+H⁺]=727.30

Conformer 35B: ESI-MS: [M+H⁺]=727.30

Example 36

N-[(3S)-5-Cyano-1-(4-cyanophenyl)sulfonyl-3-(2-ethoxyphenyl)-2-oxo-indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-(oxetan-3-yl)-piperidin-4-yl, R^{8a} is H, R^{8b} is cyano and R^{8c} is H)

ESI-MS: [M+H⁺]=722.20

Example 37

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-(oxetan-3-yl)-piperidin-4-yl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

ESI-MS: [M+H⁺]=715.30

The product was obtained in form of two conformers. These conformers were identified with following column: Zorbax Extended C18, 50 \times 2.1 mm ID, 1.8 μ m, System: ACN/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μ l Temp: 65° C.

Conformer 37A: retention time: 1.48 min

Conformer 37B: retention time: 1.82 min

The conformers were separated via preparative RP-HPLC with following column: LUNA C18 Axia 100A 5 μ 75 \times 30; flow 40 ml/min; eluent gradient H₂O/10-90% MeOH+0.1% TFA

Conformer 37A: ESI-MS: [M+H⁺]=715.30

Conformer 37B: ESI-MS: [M+H⁺]=715.30

167

Example 38

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-[1-(oxetan-3-yl)-4-piperidyl]-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-(oxetan-3-yl)-piperidin-4-yl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

ESI-MS: [M+H⁺]=711.30

The product was obtained in form of two conformers. These conformers were identified with following column: Zorbax Extended C18, 50×2.1 mm ID, 1.8μ, System: ACN/Formic acid, Flow: 0.7 ml/min, Inj. Vol: 1 μl Temp: 65° C.

Conformer 38A: retention time: 1.59 min

Conformer 38B: retention time: 1.80 min

The conformers were separated via preparative RP-HPLC with following column: LUNA C18 Axia 100A 5μ 75×30; flow 40 ml/min; eluent gradient H₂O/10-90%

MeOH+0.1% TFA

Conformer 38A: ESI-MS: [M+H⁺]=711.30

Conformer 38B: ESI-MS: [M+H⁺]=711.30

Example 39

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenyl)sulfonyl-3-(2-ethoxyphenyl)-2-oxo-indolin-3-yl]-2-(1-methyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylpiperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=715.3

The product was obtained in form of two conformers. These conformers were identified with following column: Phenomenex, Kinetex 1.7μ, 100A, C18, 50×2.1, System: MeOH/Formic acid, Flow: 0.6 ml/min, Inj. Vol: 2 μl Temp: 70° C.

Conformer 39A: retention time: 3.32 min

Conformer 39B: retention time: 4.08 min

The conformers were separated via preparative HPLC with following column: xTerra prepMS C18 19×150 mm 5 μm; flow 15 ml/min; eluent gradient H₂O/10-90% MeOH+0.1% TFA

Conformer 39A: ESI-MS: [M+H⁺]=715.30

Conformer 39B: ESI-MS: [M+H⁺]=715.30

Example 40

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=713.30

Example 41

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-2-oxo-1-(p-tolylsulfonyl)indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is methyl and R^{8c} is H)

ESI-MS: [M+H⁺]=697.30

168

The product was obtained in form of two conformers. These conformers were identified with following column: WATERS, XBridge C18, 2.5μ, 20×2.1 mm ID, System: MeOH/Formic acid, Flow: 0.6 ml/min, Inj. Vol: 3 μl Temp: 65° C.

Conformer 41A: retention time: 4.56 min

Conformer 41B: retention time: 4.74 min

Example 42

N-[(3S)-5-Cyano-1-(4-cyanophenyl)sulfonyl-3-(2-ethoxyphenyl)-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is cyano and R^{8c} is H)

ESI-MS: [M+H⁺]=708.30

The product was obtained in form of two conformers. These conformers were identified with following column: WATERS, XBridge C18, 2.5μ, 20×2.1 mm ID, System: MeOH/Formic acid, Flow: 0.6 ml/min, Inj. Vol: 3 μl Temp: 65° C.

Conformer 42A: retention time: 4.23 min

Conformer 42B: retention time: 4.63 min

Example 43

N-[(3S)-5-Cyano-3-(2-ethoxyphenyl)-1-(4-fluorophenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(1-isopropyl-4-piperidyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide; 2,2,2-trifluoroacetic acid

(S-enantiomer of compound of formula I.49, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is F and R^{8c} is H)

The product was obtained in form of two conformers. These conformers were separated with following RP-HPLC column: xTerra prepMS C18 19×150 mm 5 μm; flow 15 ml/min; eluent gradient H₂O/30-100% MeOH+0.1% TFA

Conformer 43A: retention time: 14.27 min

Conformer 43B: retention time: 18.36 min

Example 44

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-6-azaspiro[3.3]heptane-2-carboxamide

(S-enantiomer of compound of formula I.3, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

44.1 (S)-tert-Butyl 6-((5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbonyl)-2-azaspiro[3.3]heptane-2-carboxylate

N1-((Ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (5.4 mmol, 1.0 g) was added portionwise to a solution of (S)-3-amino-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindoline-5-carbonitrile (1.1 mmol, 500 mg) and 2-(tert-butoxycarbonyl)-2-azaspiro[3.3]heptane-6-carboxylic acid (1.1 mmol, 260 mg) in pyridine (10 ml). The mixture was stirred for 12 h at rt. The reaction was monitored by TLC (eluent: 5%

169

MeOH/CH₂Cl₂). The mixture was poured onto cooled water and the precipitate filtered off. It was washed with cold water and dried in vacuo. The crude product was directly used in the next step without purification.

ESI-MS: [M+H⁺]=688.20 (90% purity)

44.2 N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-6-azaspiro[3.3]heptane-2-carboxamide

(S)-tert-Butyl 6-((5-cyano-3-(2-ethoxypyridin-3-yl)-1-((4-methoxyphenyl)sulfonyl)-2-oxoindolin-3-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate (1.0 mmol, 679 mg) was dissolved in CH₂Cl₂ (10 ml) and then treated with TFA (9.9 mmol, 0.8 ml). The mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC (eluent: 5% MeOH/CH₂Cl₂). The mixture was concentrated, diluted with ethyl acetate (30 mL) and washed twice with water (20 mL each). The combined organic layers were dried (Na₂SO₄), filtered and evaporated. The residue was purified using a SiOH-Chromabond (eluent: 0-6% MeOH/CH₂Cl₂). Yield: 114 mg (20%).

ESI-MS: [M+H⁺]=588.20

Example 45

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-6-(1-isopropyl-4-piperidyl)-6-azaspiro[3.3]heptane-2-carboxamide

(S-enantiomer of compound of formula I.3, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-isopropylpiperidin-4-yl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=713.35

Example 46

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-6-(1-methylazetidyl)-6-azaspiro[3.3]heptane-2-carboxamide

(S-enantiomer of compound of formula I.3, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 1-methylazetidyl, R^{8a} is H, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: [M+H⁺]=657.20

Example 47

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-3-(piperidin-4-yl)-3-azaspiro[5.5]undecane-9-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.15, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is piperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 757.30 [M+H]⁺

Example 48

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(2,6-diazaspiro[3.3]heptan-2-yl)spiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.4, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 2,6-diazaspiro[3.3]heptane-2-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 713.30 [M+H]⁺

170

Example 49A

First stereoisomer of N-(5-cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-7-(piperidin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxamide 2,2,2-trifluoroacetate

(First stereoisomer of compound of formula I.5, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is piperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 730.30 [M+H]⁺

Example 49B

Second stereoisomer of N-(5-cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-7-(piperidin-4-yl)-2,7-diazaspiro[3.5]nonane-2-carboxamide 2,2,2-trifluoroacetate

(Second stereoisomer of compound of formula I.5, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is piperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 730.30 [M+H]⁺

Example 50

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2-(piperidin-4-yl)-2,7-diazaspiro[3.5]nonane-7-carboxamide bis-2,2,2-trifluoroacetate

(Compound of formula I.9, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is piperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 730.30 [M+H]⁺

Example 51

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,7-diazaspiro[3.5]nonane-7-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.9, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 647.20 [M+H]⁺

Example 52

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-3-azaspiro[5.5]undecane-9-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.15, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 674.30 [M+H]⁺

171

Example 53

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-9-methyl-3,9-diazaspiro[5.5]undecane-3-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.13, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is methyl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 689.30 [M+H]⁺

Example 54

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(4-ethylpiperazin-1-yl)spiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.4, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is 4-ethylpiperazin-1-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 729.20 [M+H]⁺

Example 55

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-7-methyl-2,7-diazaspiro[3.5]nonane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.5, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is methyl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 661.20 [M+H]⁺

Example 56

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-9-ethyl-3,9-diazaspiro[5.5]undecane-3-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.13, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is ethyl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 703.20 [M+H]⁺

Example 57

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2-azaspiro[3.3]heptane-6-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.3, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 618.20 [M+H]⁺

Example 58

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 619.20 [M+H]⁺

172

Example 59

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.1, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is piperidin-4-yl, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 702.30 [M+H]⁺

Example 60

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,7-diazaspiro[3.5]nonane-2-carboxamide 2,2,2-trifluoroacetate

(Compound of formula I.5, wherein X¹ is NH, R¹ is CN, R² is H, R⁵ is H, R^{8a} is methoxy, R^{8b} is methoxy and R^{8c} is H)

ESI-MS: 647.20 [M+H]⁺

III. Determination of the Biological Activity

1. Vasopressin V1b Receptor Binding Assay:

Substances:

The test substances were dissolved in a concentration of 5 mM in 100% DMSO and further diluted to 5×10⁻⁴ M to 5×10⁻⁹ M. These serial DMSO predilutions were diluted 1:10 with assay buffer. The substance concentration was further diluted 1:5 in the assay mixture resulting in 2% DMSO in the mixture. All dilutions were performed in a Biomek NX automation workstation (Beckman)

Membrane Preparation:

CHO-K1 cells with stably expressed human vasopressin V1b receptor (clone 3H2) were harvested and homogenized in 50 mM Tris-HCl and in the presence of protease inhibitors (Roche complete Mini #1836170) using a Polytron homogenizer at intermediate setting for 2×10 seconds, and subsequently centrifuged at 40 000×g for 1 h. The membrane pellet was again homogenized and centrifuged as described and subsequently taken up in 50 mM Tris-HCl, pH 7.4, homogenized and stored in aliquots frozen in liquid nitrogen at -190° C.

Binding Assay:

The binding assay was carried out by the method based on that of Tahara et al. (Tahara A et al., Brit. J. Pharmacol. 125, 1463-1470 (1998)).

The incubation buffer was: 50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4.

In the assay mixture (200 μl), membranes (26 μg protein in incubation buffer) from CHO-K1 cells with stably expressed human V1b receptors (cell line hV1b_3H2_CHO) were incubated with 1.5 nM ³H-AVP (8-Arg-vasopressin, PerkinElmer, NET 800) in incubation buffer (50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4) (total binding) or additionally with increasing concentrations of test substance (displacement experiment). The nonspecific binding was determined with 1 μM AVP (Fluka 94836). All determinations were carried out as duplicate determinations. After incubation (60 minutes at room temperature), the free radioligand was filtered off by vacuum filtration (Tomtec Mach III) through Wathman GF/B glass fiber filter plates (UniFilter, PerkinElmer 6005177). The liquid scintillation measurement took place in a Microbeta TriLux 12 (Wallac).

Analysis:

The binding parameters were calculated by nonlinear regression in SAS. The algorithms of the program operate in analogy to the LIGAND analysis program (Munson P J and Rodbard D, Analytical Biochem. 107, 220-239 (1980)). The Kd of ³H-AVP for the recombinant human V1b receptors is 0.4 nM and was used to determine the Ki.

2. Vasopressin V1a Receptor Binding Assay:

Substances:

The test substances were dissolved in a concentration of 5 mM M in DMSO. Further dilution of these DMSO solutions took place as described for V1b.

Membrane Preparation:

CHO-K1 cells with stably expressed human vasopressin V1a receptor (clone 5) were harvested and homogenized in 50 mM Tris-HCl and in the presence of protease inhibitors (Roche complete Mini #1836170) using a Polytron homogenizer at intermediate setting for 2×10 seconds, and subsequently centrifuged at 40 000×g for 1 h. The membrane pellet was again homogenized in a High-Pressure-Homogenizer, Polytec 50K at 1500 PSI (Heinemann, Germany) and subsequently taken up in 50 mM Tris-HCl, pH 7.4, homogenized and stored in aliquots frozen in liquid nitrogen at -190° C.

Binding Assay:

The binding assay was carried out by the method based on that of Tahara et al. (Tahara A et al., Brit. J. Pharmacol. 125, 1463-1470 (1998)).

The incubation buffer was: 50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4.

In the assay mixture (200 µl), membranes (40 µg protein in incubation buffer) from CHO-K1 cells with stably expressed human V1a receptors (cell line hV1a_5_CHO) were incubated with 0.04 nM ¹²⁵I-AVP (8-Arg-vasopressin, PerkinElmer NEX 128) in incubation buffer (50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4) (total binding) or additionally with increasing concentrations of test substance (displacement experiment). The nonspecific binding was determined with 1 µM AVP (Fluka 94836). Duplicate determinations were carried out.

After incubation (60 minutes at room temperature), the samples were processed as described for V1b.

Analysis:

The binding parameters were calculated by nonlinear regression in SAS. The algorithms of the program operate in analogy to the LIGAND analysis program (Munson P J and Rodbard D, Analytical Biochem. 107, 220-239 (1980)). The Kd of ¹²⁵I-AVP for the recombinant hV1a receptors was determined in saturation experiments. A Kd of 1.33 nM was used to determine the Ki.

3. Oxytocin Receptor Binding Assay

Substances:

The substances were dissolved in a concentration of 5 mM in DMSO and diluted further as described for V1b.

Membrane Preparation:

Confluent HEK-293 cells with transiently expressing recombinant human oxytocin receptors were centrifuged at 750×g at room temperature for 5 minutes. The residue was taken up in ice-cold lysis buffer (50 mM Tris-HCl, 10% glycerol, pH 7.4 and Roche complete protease inhibitor) and subjected to an osmotic shock at 4° C. for 20 minutes. Cell lysates were then centrifuged at 750×g at 4° C. for 20 minutes, the residue was taken up in incubation buffer (50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4), and aliquots corresponding to 10⁷ cells/ml were prepared. The aliquots were frozen at -80° C. until use.

Binding Assay:

On the day of the experiment, the cell lysate was thawed, homogenized, and diluted with incubation buffer (50 mM Tris, 10 mM MgCl₂, 0.1% BSA, pH 7.4) to the desired concentration. The reaction mixture of 0.200 ml was composed of cell lysate corresponding to 5×10⁴ cells (HEK-293 cells expressing transiently human OT receptors) and 1 nM ³H-oxytocin (PerkinElmer NET858) in the presence of test substance (displacement experiment) or incubation buffer only (total binding). The nonspecific binding was determined in the presence of 1 µM oxytocin (Bachem AG, H2510). Determinations were carried out in duplicates. After 60 minutes incubation at room temperature, bound and free radioligand were separated by filtration under vacuum on GF/B UniFilter plates (Perkin Elmer #6005177) pre-incubated with 0.3% PEI. The bound radioactivity was determined by liquid scintillation measurement in a Microbeta (Perkin Elmer) plate counter.

Analysis:

The binding parameters were calculated by nonlinear regression analysis (SAS) in analogy to the LIGAND program of Munson and Rodbard (Analytical Biochem 1980; 107: 220-239). The Kd of ³H-oxytocin for the recombinant human OT receptors was 7.6 nM and was used to calculate the Ki from competition binding experiments.

4. Determination of the Microsomal Half-life:

The metabolic stability of the compounds of the invention was determined in the following assay.

The test substances were incubated in a concentration of 0.5 µM as follows:

0.5 µM test substance are preincubated together with liver microsomes from different species (from rat, human or other species) (0.25 mg of microsomal protein/ml) in 0.05 M potassium phosphate buffer of pH 7.4 in microtiter plates at 37° C. for 5 min. The reaction is started by adding NADPH (1 mg/mL). After 0, 5, 10, 15, 20 and 30 min, 50 µl aliquots are removed, and the reaction is immediately stopped and cooled with the same volume of acetonitrile. The samples are frozen until analyzed. The remaining concentration of undegraded test substance is determined by MSMS. The half-life (T_{1/2}) is determined from the gradient of the signal of test substance/unit time plot, it being possible to calculate the half-life of the test substance, assuming first order kinetics, from the decrease in the concentration of the compound with time. The microsomal clearance (mCl) is calculated from $mCl = \ln 2 / T_{1/2} / (\text{content of microsomal protein in mg/ml}) \times 1000$ [ml/min/mg] (modified from references: Di, The Society for Biomolecular Screening, 2003, 453-462; Obach, D M D, 1999 vol 27. N 11, 1350-1359).

5. Methods for in vitro Determination of the Cytochrome P450 (CYP) Inhibition

Luminescent Substrates for 2C9 and 3A4:

0.4 mg/ml human liver microsomes are preincubated with the test substances to be investigated (0-20 µM), the CYP-specific substrates, in 0.05 M potassium phosphate buffer of pH 7.4 at 37° C. for 10 min. The Cyp-specific substrate for CYP 2C9 is luciferin H, and for CYP 3A4 is luciferin BE. The reaction is started by adding NADPH. After incubation at RT for 30 min, the luciferin detection reagent is added, and the resulting luminescence signal is measured (modified from reference: Promega, Technical Bulletin P450-GLO™ Assays).

Midazolam CYP 3A4 Time-dependent Inhibition

The assay consists of 2 parts. Firstly, the test substance is preincubated with the liver microsomes (with NADPH=preincubation, then addition of the substrate; in the second part the substrate and the test substance are added simultaneously=coincubation.

Preincubation:

0.05 mg/ml microsomal protein (human liver microsomes) are preincubated with 0-10 μ M (or 50 μ M) test substance in 50 mM potassium phosphate buffer for 5 min. The reaction is started with NADPH. After 30 min 4 μ M midazolam (final concentration) are added, and incubation is continued for 10 min. 75 μ l of the reaction solution are removed after 10 min, and stopped with 150 μ l of acetonitrile solution.

Coincubation:

0.05 mg/ml microsomal protein (human liver microsomes) are preincubated with 4 μ M midazolam (final concentration) and 0-10 μ M (or 50 μ M) test substance in 50 mM potassium phosphate buffer for 5 min. The reaction is started with NADPH. 75 μ l of the reaction solution are removed after 10 min and stopped with 150 μ l of acetonitrile solution. The samples are frozen until the MSMS analysis (modified from references: Obdach, Journal of Pharmacology & Experimental Therapeutics, Vol 316, 1, 336-348, 2006; Walsky, Drug Metabolism and Disposition Vol 32, 6, 647-660, 2004).

6. Method for Determining the Solubility in Water (in mg/ml)

The solubility in water of the compounds of the invention can be determined for example by the so-called shake flask method (as specified in *ASTM International: E 1148-02, Standard test methods for measurement of aqueous solubility, Book of Standards Volume 11.05.*). This entails an excess of the solid compound being put into a buffer solution with a particular pH (for example phosphate buffer of pH 7.4), and the resulting mixture being shaken or stirred until equilibrium has been set up (typically 24 or 48 hours, sometimes even up to 7 days). The undissolved solid is then removed by filtration or centrifugation, and the concentration of the dissolved compound is determined by UV spectroscopy or high pressure liquid chromatography (HPLC) by means of an appropriate calibration plot.

7. Results

The results of the receptor binding investigations are expressed as receptor binding constants [K_i (V1b)] or selectivities [K_i (V1a)/ K_i (V1b)]. The results of the investigation of the metabolic stability are indicated as microsomal clearance (mCl).

The compounds of the invention show very high affinities for the V1b receptor in these assays (maximally 100 nM, or maximally 10 nM, frequently <1 nM). The compounds also show high selectivities vis-à-vis the V1a receptor and a good metabolic stability, measured as microsomal clearance.

The results are listed in table C. The numbers of the compounds refer to the synthesis examples.

TABLE C

Example	K_i (h-V1b)* [nM]	K_i (h-V1a)/ K_i (h-V1b)
1	++	+++
1B	+++	+++
2	+	+++
3	++	+++
4	++	+++
5	+	+++
6	++	++
7	++	++
8	+	++
9	++	+++
10	++	++
11	++	+++
12	++	+
13	+++	++

TABLE C-continued

Example	K_i (h-V1b)* [nM]	K_i (h-V1a)/ K_i (h-V1b)
14	+	+++
15	+++	+++
16	++	++
17	++	++
18	+++	+++
19	++	+++
20	++	++
20A	++	++
21A	+	+++
21B	+	+++
22	++	+++
24	+	+++
25	+	++
27	+	+++
29	++	+++
31	+	
32	+	++
33	+	++
35B	+	++
39B	+	++
40	++	+++
41	+	+++
42	+	+++
43B	+	+++
44	+	
45	+	+
46	++	+
47	++	
48	++	
50	+	
51	+	
52	++	
53	+	
54	+++	
55	+	
56	+	
57	+	
58	+	++
59	+	+++
60	++	++

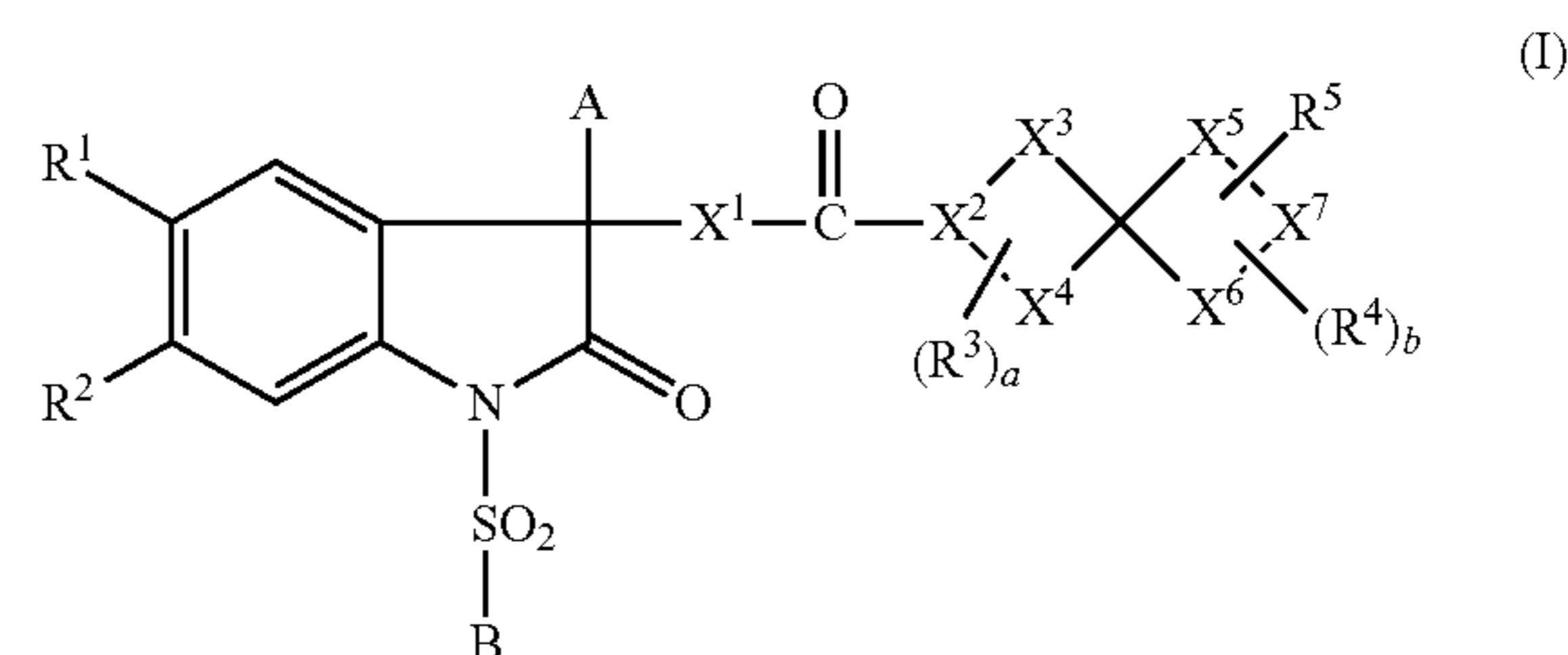
*h = human

Key:

	K_i (h-V1b)	K_i (h-V1a)/ K_i (h-V1b)
+	>10-100 nM	10-<25
++	1-10 nM	25-75
+++	<1 nM	>75

The invention claimed is:

1. A compound of formula I



wherein

A is a ring selected from the group consisting of phenyl and 6-membered hetaryl containing 1 or 2 nitrogen atoms as ring members, where ring A carries one substituent R^6 and optionally one substituent R^7 ;

B is a ring selected from the group consisting of phenyl, pyridyl and quinolinyl, where ring B may carry 1, 2 or 3 substituents R⁸;

X¹ is NH, CH₂ or O;

X² is N or CH;

X³, X⁴, X⁵ and X⁶, independently of each other, are selected from the group consisting of —CH₂—, —O—, —S(O)_c—, —NH—, —C(O)—, —CH₂CH₂—, —CH₂O—, —OCH₂—, —S(O)_cCH₂—, —CH₂S(O)_c—, CH₂NH—, —NHCH₂—, —CH₂C(O)— and —C(O)CH₂—;

X⁷ is NH, CH₂ or O;

R¹ is selected from the group consisting of cyano, halogen, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R² is selected from the group consisting of hydrogen, cyano, halogen, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₃-C₆-cycloalkyl, fluorinated C₃-C₆-cycloalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R³ and R⁴, independently of each other and independently of each occurrence, are selected from the group consisting of hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and NR⁹R¹⁰, and in case that R³ or R⁴ are bound to a carbon ring atom, are additionally selected from halogen; or

two non-geminal radicals R³ form together a group —(CH₂)_k—, where k is 1, 2, 3 or 4, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two non-geminal radicals R⁴ form together a group —(CH₂)_k—, where k is 1, 2, 3 or 4, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two geminal radicals R³ form together a group —(CH₂)_j—, where j is 2, 3, 4 or 5, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group; or

two geminal radicals R⁴ form together a group —(CH₂)_j—, where j is 2, 3, 4 or 5, where 1 or 2 hydrogen atoms in this group may be replaced by a methyl group;

with the proviso that R³ and R⁴ are not halogen, hydroxyl, C₁-C₄-alkoxy or C₁-C₄-haloalkoxy if they are bound to a carbon atom in α-position to a nitrogen ring atom;

R⁵ is selected from the group consisting of hydrogen; cyano; C₁-C₆-alkyl; C₂-C₆-alkenyl; C₂-C₆-alkynyl; C₃-C₇-cycloalkyl, where the four last-mentioned radicals may be partially or fully halogenated and/or may carry one or more substituents R¹¹; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; —OR¹³; —S(O)₁R¹³; NR¹⁴R¹⁵; and —C(=O)R¹⁶;

R⁶ and R⁷, independently of each other, are selected from the group consisting of halogen, cyano, hydroxyl, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

each R⁸ is independently selected from the group consisting of halogen, cyano, hydroxyl, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-hydroxyalkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy;

R⁹ and R¹⁰, independently of each other, are selected from the group consisting of hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₄-alkyl, phenyl and benzyl;

each R¹¹ is independently selected from the group consisting of cyano; —OR¹³; —S(O)₁R¹³; NR¹⁴R¹⁵; —C(=O)R¹⁶; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and as a substituent on a cycloalkyl ring, R¹¹ is additionally selected from C₁-C₄-alkyl or C₁-C₄-haloalkyl;

each R¹² is independently selected from the group consisting of halogen; hydroxyl; cyano; nitro; C₁-C₄-alkyl; C₁-C₄-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-alkylthio; C₁-C₄-haloalkylthio; C₁-C₄-alkylsulfinyl; C₁-C₄-haloalkylsulfinyl; C₁-C₄-alkylsulfonyl; C₁-C₄-haloalkylsulfonyl; phenyl; phenoxy; benzyloxy, where the phenyl moiety in the three last-mentioned radicals may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy;

each R¹³ is independently selected from the group consisting of hydrogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; C₁-C₄-alkyl which carries one substituent R¹⁷; C₂-C₄-alkenyl; C₂-C₄-haloalkenyl; C₂-C₄-alkynyl; C₂-C₄-haloalkynyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; phenyl which may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heterocyclic ring may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy;

R¹⁴ and R¹⁵, independently of each other and independently of each occurrence, are selected from the group consisting of hydrogen; C₁-C₄-alkyl; C₁-C₄-haloalkyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; phenyl which may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heterocyclic ring may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy, C₁-C₄-alkylcarbonyl and C₁-C₄-haloalkylcarbonyl; each R¹⁶ is independently selected the group consisting of from hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-halocycloalkyl, phenyl, —OR¹³ and NR¹⁴R¹⁵;

each R¹⁷ is independently selected from the group consisting of cyano; hydroxyl; C₁-C₄-alkoxy; C₁-C₄-haloalkoxy; C₁-C₄-alkylthio; C₁-C₄-haloalkylthio; C₁-C₄-alkylsulfinyl; C₁-C₄-haloalkylsulfinyl; C₁-C₄-alkylsulfonyl; C₁-C₄-haloalkylsulfonyl; NR¹⁴R¹⁵; C₁-C₄-alkylcarbonyl; C₁-C₄-haloalkylcarbonyl; C₃-C₆-cycloalkyl; C₃-C₆-halocycloalkyl; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²;

a is 0, 1 or 2;

b is 0, 1 or 2;

c is 0, 1 or 2; and

l is 0, 1 or 2;

or an N-oxide, stereoisomer, or pharmaceutically acceptable salt thereof, or wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope.

2. The compound as claimed in claim 1, wherein at least one hydrogen atom has been replaced by a deuterium atom.

3. The compound as claimed in claim 1, where X¹ is NH or CH₂.

4. The compound as claimed in claim 1, where X³, X⁴, X⁵ and X⁶, independently of each other, are selected from the group consisting of —CH₂— and —CH₂CH₂—.

5. The compound as claimed in claim 1, where X⁷ is NH or CH₂.

6. The compound as claimed in claim 1, where R⁵ is bound to X⁷.

7. The compound as claimed in claim 1, where A is phenyl or pyridyl, where A carries one substituent R⁶ and optionally one substituent R⁷.

8. The compound as claimed in claim 7, where A is phenyl or 3-pyridyl, where A carries the radical R⁶ in 2-position and the radical R⁷, if present, in 4- or 5-position, relative to the 1-position of the attachment point of A to the remainder of the molecule.

9. The compound as claimed in claim 7, where A is phenyl or 3-pyridyl, where A carries the radical R⁶ in 2-position and no radical R⁷.

10. The compound as claimed in claim 1, where B is phenyl or 2-pyridyl, where B may carry 1, 2 or 3 substituents R⁸.

11. The compound as claimed in claim 1, where R¹ is halogen or cyano.

12. The compound as claimed in claim 11, where R¹ is selected from the group consisting of cyano, fluorine and chlorine.

13. The compound as claimed in claim 1, where R² is hydrogen or halogen.

14. The compound as claimed in claim 1, where R³ and R⁴, independently of each other and independently of each occurrence, are selected from the group consisting of halogen and C₁-C₄-alkyl, with the proviso that R³ and R⁴ are not halogen if they are bound to a carbon atom in α -position to a nitrogen ring atom.

15. The compound as claimed in claim 1, where R⁵ is selected from the group consisting of hydrogen; C₁-C₆-alkyl; fluorinated C₁-C₆-alkyl; C₃-C₆-cycloalkyl; fluorinated C₃-C₆-cycloalkyl; C₁-C₆-alkyl which carries one substituent R¹¹; phenyl which may carry 1, 2 or 3 substituents R¹²; a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated, partially unsaturated or maximally unsaturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that R⁵ is bound to a carbon ring atom, it is additionally selected from —OR¹³.

16. The compound as claimed in claim 15, where R⁵ is selected from the group consisting of hydrogen; C₁-C₆-alkyl; fluorinated C₁-C₆-alkyl; C₁-C₆-alkyl which carries one substituent R¹¹; a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members; and a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and in case that R⁵ is bound to a carbon ring atom, it is additionally selected from —OR¹³.

17. The compound as claimed in claim 16, where R⁵ is selected from the group consisting of hydrogen; C₁-C₄-alkyl; C₁-C₄-alkyl which carries one substituent R¹¹; a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of O, N and S as ring members; and a 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic spiro ring containing 1 or 2 heteroatoms selected from the group consisting of O, N and S as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1 or 2 substituents R¹²; and in case that R⁵ is bound to a carbon ring atom, it is additionally selected from —OR¹³.

18. The compound as claimed in claim 1, where R¹¹ is selected from the group consisting of cyano; —OR¹³; NR¹⁴R¹⁵; a 3-, 4-, 5-, 6- or 7-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N,

181

S, NO, SO and SO₂ as ring members; and a 5-, 6-, 7-, 8-, 9-, 10- or 11-membered saturated heterobicyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic or heterobicyclic ring may carry 1, 2 or 3 substituents R¹²; and as a substituent on a cycloalkyl ring, R¹¹ is additionally selected from the group consisting of C₁-C₄-alkyl and C₁-C₄-haloalkyl.

19. The compound as claimed in claim 18, where R¹¹ is NR¹⁴R¹⁵, where R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen and C₁-C₄-alkyl; or a 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1 or 2 or 3 substituents R¹².

20. The compound as claimed in claim 1, where R¹² is selected from the group consisting of halogen; cyano; C₁-C₄-alkyl; fluorinated C₁-C₄-alkyl; C₁-C₄-alkoxy; fluorinated C₁-C₄-alkoxy; phenyl which may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, C₁-C₄-alkoxy and fluorinated C₁-C₄-alkoxy; and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members, where the heteromonocyclic ring may carry 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxyl, cyano, C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, C₁-C₄-alkoxy and fluorinated C₁-C₄-alkoxy.

21. The compound as claimed in claim 20, where R¹² is selected from the group consisting of C₁-C₄-alkyl, fluorinated C₁-C₄-alkyl, and a 3-, 4-, 5- or 6-membered saturated heteromonocyclic ring containing 1 or 2 heteroatoms selected from the group consisting of O, N and S as ring members.

22. The compound as claimed in claim 1, where R¹³ is selected from the group consisting of hydrogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and C₁-C₄-alkyl which carries one substituent R¹⁷.

23. The compound as claimed in claim 1, where R¹⁷ is selected from NR¹⁴R¹⁵; phenyl which may carry 1, 2 or 3 substituents R¹²; and a 3-, 4-, 5-, 6- or 7-membered saturated, partially unsaturated or maximally unsaturated heteromonocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom groups selected from the group consisting of O, N, S, NO, SO and SO₂ as ring members.

24. The compound as claimed in claim 1, where R⁶ is C₁-C₃-alkoxy.

25. The compound as claimed in claim 1, where R⁷ is halogen or C₁-C₃-alkoxy.

26. The compound as claimed in claim 1, where each R⁸ is independently selected from the group consisting of halogen, cyano, C₁-C₃-alkyl, fluorinated C₁-C₃-alkyl, C₁-C₃-alkoxy and fluorinated C₁-C₃-alkoxy.

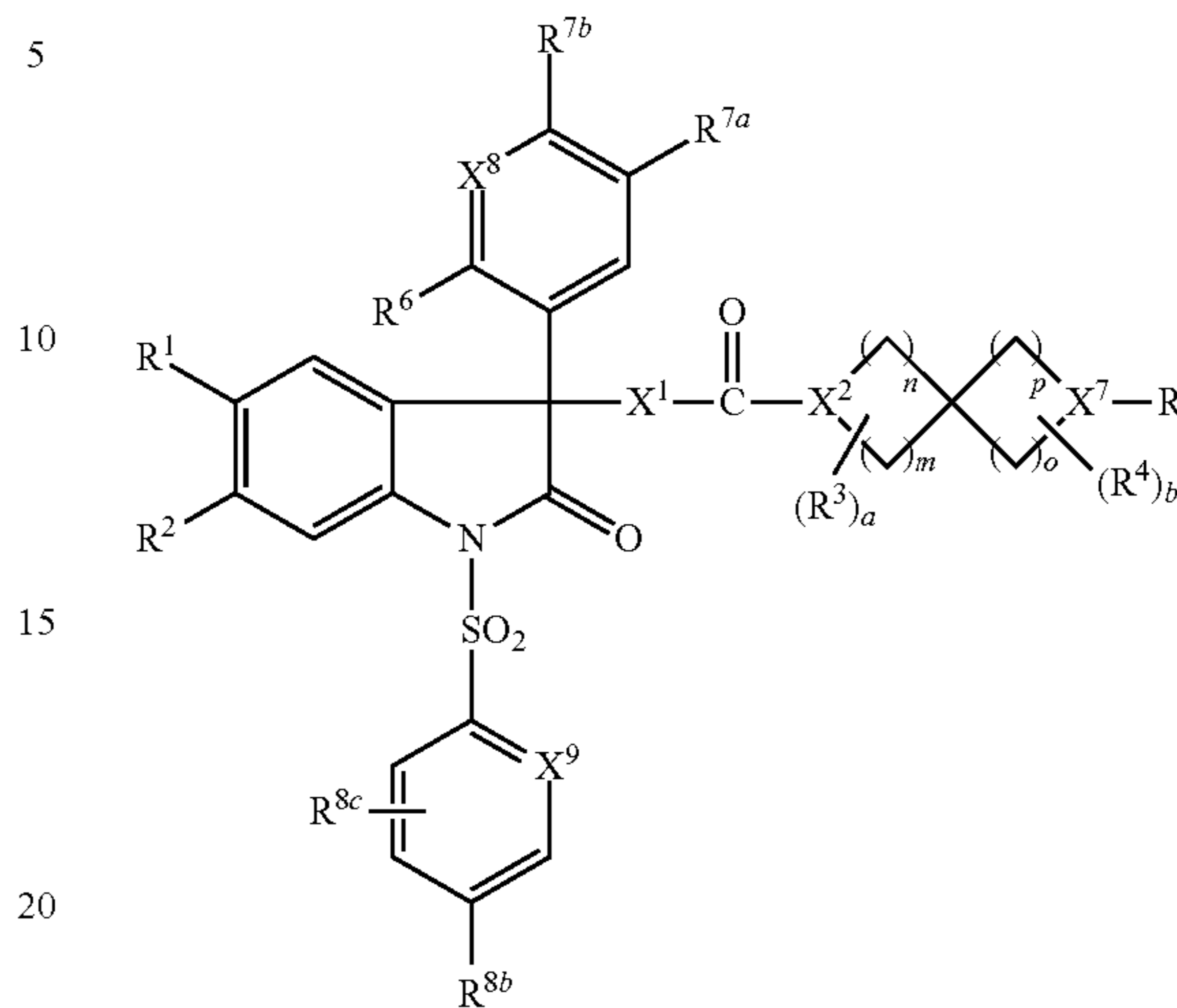
27. The compound as claimed in claim 26, where each R⁸ is independently selected from the group consisting of fluorine, cyano, methyl, methoxy and trifluoromethoxy.

28. The compound as claimed in claim 1, where a and b are independently 0 or 1.

182

29. The compound as claimed in claim 1, of formula IA

(IA)



where

X¹, X², X⁷, R¹, R², R³, R⁴, R⁵, R⁶, a and b are as defined in claim 1;

X⁸ is N or CH;

X⁹ is N or C—R^{8a};

R^{7a} and R^{7b}, independently of each other, are hydrogen or have one of the definitions given for R⁷ in claim 1, with the proviso that at least one of R^{7a} and R^{7b} is hydrogen; R^{8a}, R^{8b} and R^{8c}, independently of each other, are hydrogen or have one of the definitions given for R⁸ in claim 1; and

m, n, o and p are independently of each other 1 or 2.

30. The compound as claimed in claim 29, where m and n are both 1 or are both 2.

31. The compound as claimed in claim 29, where o and p are both 1 or are both 2.

32. A compound selected from the group consisting of: N-[5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3R)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(3-morpholinopropyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(3-morpholinopropyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3R)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(3-morpholinopropyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluoro-2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3S)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluoro-2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3R)-5-Cyano-3-(2-ethoxy-3-pyridyl)-1-(4-fluoro-2-methoxyphenyl)sulfonyl-2-oxo-indolin-3-yl]-2-(2-morpholinoethyl)-2,6-diazaspiro[3.3]heptane-6-carboxamide;

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-2,6-diazaspiro[3.3]heptane-2-carboxamide;

N-[(3R)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-2,6-diazaspiro[3.3]heptane-2-carboxamide;

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide;

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide;

N-[(3R)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-6-(piperidin-4-yl)-2,6-diazaspiro[3.3]heptane-2-carboxamide;

N-(5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl)-2,7-diazaspiro[3.5]nonane-2-carboxamide;

N-[(3S)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-2,7-diazaspiro[3.5]nonane-2-carboxamide; and

N-[(3R)-5-Cyano-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxoindolin-3-yl]-2,7-diazaspiro[3.5]nonane-2-carboxamide;

or an N-oxide, stereoisomer, and or pharmaceutically acceptable salt thereof, or wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope.

33. A pharmaceutical composition comprising at least one compound of the formula I as defined in claim 1 and/or an N-oxide, a stereoisomer or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

34. A method for the treatment of vasopressin-related diseases comprising administering a compound of claim 1, or an N-oxide, a stereoisomer or pharmaceutically acceptable salt thereof, to a subject in need thereof.

35. The method as claimed in claim 34, wherein the vasopressin-related diseases are selected from the group consisting of diabetes; insulin resistance; nocturnal enuresis; incontinence and diseases in which impairments of blood clotting occur; hypertension; pulmonary hypertension; heart failure; myocardial infarction; coronary spasm; unstable angina; PTCA (percutaneous transluminal coronary angioplasty); ischemias of the heart; impairments of the renal system; edemas; renal vasospasm; necrosis of the renal cortex; hyponatremia; hypokalemia; Schwartz-Bartter syndrome; impairments of the gastrointestinal tract; gastritis; vasospasm; hepatocirrhosis; gastric and intestinal ulcers; emesis; emesis occurring during chemotherapy; travel sickness; affective disorders; Alzheimer's disease; mild cognitive impairment and cognitive impairment associated with schizophrenia, aging, Alzheimer disease, Parkinson's disease and/or dementia; increased aggression in conditions selected from the group consisting of Alzheimer's disease, schizophrenia, bipolar disorder, frontal lobe injuries and substance use disorders; Cushing's syndrome and stress-dependent diseases; sleep disorders; vasomotor symptoms;

thermoregulatory dysfunctions; substance-related and addictive disorders; schizophrenia and psychosis; pain; and micturition disorders.

36. The method as claimed in claim 35, where the affective disorders are selected from the group consisting of depressive disorders, anxiety disorders and stress-dependent anxiety disorders; where the substance-related and addictive disorders are selected from the group consisting of alcohol use disorder, alcohol intoxication, and alcohol withdrawal.

37. The method as claimed in claim 35, where the affective disorders are selected from the group consisting of depressive disorders, anxiety disorders, obsessive-compulsive disorders, trauma and stressor-related disorders; and bipolar disorders;

where substance-related and addictive disorders are selected from the group consisting of substance use disorder, substance-induced disorder, alcohol use disorder, alcohol intoxication, alcohol withdrawal, caffeine intoxication, caffeine withdrawal, cannabis use disorder, cannabis withdrawal, phencyclidine use disorder, other hallucinogen use disorders, phencyclidine intoxication, other hallucinogen disorders, hallucinogen persisting perception disorder, inhalant use disorder, inhalant intoxication, opioid use disorder, opioid withdrawal, sedative, hypnotic or anxiolytic use disorder, sedative, hypnotic or anxiolytic withdrawal, stimulant use disorder, stimulant intoxication, stimulant withdrawal, tobacco use disorder, tobacco withdrawal, and gambling disorder.

38. The method as claimed in claim 37, where the depressive disorders are selected from the group consisting of dysthymic disorders, major depression, seasonal depression, treatment-resistant depression disorders, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder and childhood onset mood disorders; where

the anxiety disorders are selected from the group consisting of phobias, specific phobias, general anxiety disorders, panic disorders, drug withdrawal-induced anxiety disorders, separation anxiety disorder, selective mutism, social anxiety disorder, agoraphobia, and substance/medication-induced anxiety disorder; the obsessive-compulsive are selected from the group consisting of obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder, and substance/medication-induced obsessive-compulsive disorder;

the trauma and stressor-related disorders are selected from the group consisting of reactive attachment disorder, disinhibited social engagement disorder, post-traumatic stress disorder, acute stress disorder, and adjustment disorder; and

the bipolar disorders are selected from the group consisting of bipolar I disorder, bipolar II disorder, cyclothymic disorder, and substance/medication-induced bipolar disorder.

* * * * *